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A MANUAL OF ORGANIC CHEMISTRY

FOR ADVANCED STUDENTS

VOLUME I

THE COMPOUNDS OF CARBON, HYDROGEN, OXYGEN AND THE HALOGENS

By the same author

A NEW NOTATION AND ENUMERATION
SYSTEM FOR ORGANIC COMPOUNDS
Second Edition with Diagrams

A MANUAL OF ORGANIC CHEMISTRY

FOR ADVANCED STUDENTS

by

G. MALCOLM DYSON

M.A.(OXON.), D.SC., PH.D.(LOND.), F.R.I.C., M.I.CHEM.E.

VOLUME ONE

The Compounds of Carbon,
Hydrogen, Oxygen
and the Halogens

LONGMANS, GREEN AND CO
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55 FIFTH AVENUE NEW YORK 3

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215 VICTORIA STREET TORONTO 1

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BOMBAY CALCUTTA MADRAS

First Published 1950

PRINTED IN GREAT BRITAIN AT
THE UNIVERSITY PRESS
ABERDEEN

TO

MY WIFE

WITHOUT HER CONSTANT HELP AND ENCOURAGEMENT
THIS BOOK COULD NOT HAVE BEEN WRITTEN

GENERAL PREFACE

This work is the result of an attempt to provide the student specialising in organic chemistry with a fairly comprehensive account of the subject; such an account as will serve as a guide during the final years of graduation and during the first few years of post-graduate research or teaching. A manual of this character has been needed for some time; one in which the various topics of organic chemistry are discussed at greater length than is possible in the usual student's single volume text-book, but not so extensively as in the fully documented specialist monographs. This gap in chemical literature has to a limited extent been filled by Dr. A. W. Stewart's "Recent Advances in Organic Chemistry"—an inspiring account of more recent progress in certain fields; the present work, to be completed in three volumes, is written with wider terms of reference.

The present volume deals with the compounds of carbon with hydrogen, oxygen and the halogens. The second volume, now in active preparation, deals with organic compounds in which nitrogen, sulphur, phosphorus or metallic elements are present. Volume III is devoted to considerations of the more theoretical aspects of the science. The scope of the manual has no reference to syllabuses or examinations; the guiding principle of its composition has been to include a discussion of all topics of organic chemistry, interesting to the practitioner of that subject, sufficient to enable him to obtain a working knowledge of the subdivision in question.

A word of explanation is needed in respect of the Appendices; in some instances important subjects have been dealt with rather more fully than the systematic development of the main portion of the chapter allows. In other cases, a brief summary is given of topics which are of interest to an organic chemist, but which lie on the borderland of his subject.

References to original literature have been carefully selected; they refer either to the first discovery of a substance or the earliest discussion of a topic or, again, to summaries or individual papers of importance. At the end of each chapter an appendix gives a list of books, reviews and summaries which may be consulted by those wishing to know more of the subject. These bibliographies are in no sense exhaustive, serving only to guide the reader to wider horizons; they make no attempt to usurp the proper province of the fully documented monograph.

I have consulted many standard works of reference, and have checked most of the primary sources, but owing to the present difficulties some secondary sources have, perforce, been used. I shall, therefore, be glad to hear of and to acknowledge any corrections which may usefully be incorporated in subsequent editions.

It is with great pleasure that I acknowledge the considerable debt which I owe to many of my colleagues in Loughborough; to Miss B. Fenwick, our librarian, for typing the drafts; to Dr. J. M. Connolly and Mr. E. Vero for reading the drafts and proofs; and to Dr. A. E. Dunstan for permission to use the *table* facing p. 80.

G. M. D.

Loughborough,
1948.

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CHAPTER I

INTRODUCTION

> " The Devil may write chemical textbooks, because every few years the whole thing changes."
>
> —BERZELIUS.

The study of organic chemistry is concerned with the elucidation of the structure of organic substances, with their synthesis, their transformations and reactions. Nature has elaborated countless organic types which serve as the raw materials of the organic chemist, and to these man has added a certain limited number of materials, such as coal-tar, which may be regarded as natural raw materials ' once-removed '.

In the early phases of the evolution of organic chemistry, attention was focussed on the *extraction* of principles ; dyes from woods and berries ; medicinal products from similar sources ; essential oils from flowers and fruit ; sugar from the cane ; starch from tubers ; tannins from barks and seeds ; this extraction motive has persisted right up to the present day, and still new types and materials are being wrung from natural materials by more searching examinations, witness the hormones, vitamins, auxins and similar bodies. Thus, a history of the study of plant juices shows the progressive extraction of sugars, bases such as betaines, and finally substances of the auxin type ; each step forward implies the recognition, isolation and characterisation of substances which are present in smaller and smaller proportions. There is, therefore, to be recognised a large array of individual chemical substances which occur in nature, or as the result of natural processes. The extraction of such substances in a state of purity constitutes a large section of chemical technology, one substance alone in some cases (e.g. sucrose) being responsible for a whole industry.

The isolation of pure substances from natural sources leads logically to a study of their properties and simple reactions, and through them to the recognition of structurally related groups Thus, benzoic acid from natural gums, distilled with soda-lime, yields benzene identical with that from coal-tar ; benzene can be converted readily to aniline identical with that obtained by Unverdorben in 1826 from the destructive distillation of indigo ; benzaldehyde from the essential oil of almonds can be related easily to benzoic acid. In this way the knowledge that natural products form closely related groups led to the formulation, *via* the ' theory of types ', of the products themselves and, once their structure had been established, to their synthesis from more readily accessible substances, either for the purpose of confirming the structural hypotheses, or, later, as a more economic method for their industrial production. Indigo is a case in point where the earlier synthesis established the structure, those devised later providing a cheaper and more convenient method of manufacture than the cultivation of the plant.

During the investigations outlined in previous paragraphs, organic substances not encountered in nature were frequently produced either as intermediates in the synthesis of naturally occurring materials or in abortive attempts to obtain them. These substances often proved to have desirable properties, and to offer inducement to the investigators to prepare other members of the same series, despite the absence of any natural counterparts. Examples are the discovery by W. H. Perkin (Senr.) of the simple aniline dyes in abortive attempts to make quinine, and the discovery of saccharin by Remsen and Fahlberg. It was in this way that the organic chemists were tempted to enter fresh fields and to elaborate and investigate such substances as dyes, synthetic drugs and plastics having no natural occurrence. In some cases these fields have again in turn given rise to new industries, such as the " artificial " or so-called " synthetic " dyes. It may be remarked in passing that the chemist should use care in employing the word ' synthetic ', which has two senses (*a*) as in the expression ' synthetic adrenaline ', which is taken to imply a product produced artificially from simple sources, but which is in fact identical in all respects with the adrenaline found in nature, and (*b*) as in the term ' synthetic dye ' or ' synthetic perfume ' where the dye or perfume is built up by synthesis as an imitation of or even improvement on some naturally occurring product to which it may have no structural relation. It would be convenient to restrict the word to the former use, but custom has sanctioned both usages.

Two extensive fields, therefore, of synthetic organic chemistry exist, one concerned with natural products and the other with those products which have no natural counterparts. The two fields are, of course, closely interwoven, and it is not easy to get very far away from the structures so lavishly elaborated by nature ; highly condensed aromatic ring systems built up as dyestuffs are often not very far removed from steroid substances ; artificially produced medicinal compounds frequently have structural similarity to natural substances, and very few organic types are not represented amongst natural products ; in fact, the field of purely synthetic types is getting gradually smaller —substances such as thiazoles, thought at one time to have only academic interest, are discovered as parts of the vitamin B complex and of penicillin ; arylthiocarbimides occur in the natural oils of such plants as watercress and many crucifers ; and there must still be many substances yet to be isolated and characterised in the biochemical field which will even further decrease the gap.

Organic chemistry may therefore be divided as a subject for study into the following parts :—

(1) The methods of extraction and structural elucidation of naturally occurring substances.
(2) The reactions of these materials.
(3) The transformation of the compounds of (1) into other types.
(4) The theories arising from the study of organic substances.

Thus, the organic chemist is provided with a limited number of raw materials, animal and vegetable tissues, sugar, starches, petroleum, mineral carbonates, coal, alkaloids, sterols, fats, waxes, resins and terpenes, guano and wood from which, with the aid of simple inorganic substances, all his products must be prepared. This point must always be in front of the practical organic chemist, since all synthesised substances have ultimately to be obtained from these raw materials.

This book has been written in three parts ; the first two volumes deal with the materials of the subject, the types of compounds met with in nature, how their structure has been elucidated, and how they and their analogues may be synthesised. The third volume deals with the reactions of organic chemistry, their mechanism and with special problems related to structure. This somewhat arbitrary division causes certain difficulties of arrangement, but it is presumed that the reader has already acquired some knowledge of the subject up to a standard represented by the late Professor Cohen's " Introduction to Organic Chemistry " (which has been revised by Dr. Austin). Thus, for example, in dealing in this volume with many substances which show optical activity, it will be assumed that the reader possesses an elementary knowledge of this phenomenon, although consideration of detailed problems of stereochemistry will be postponed to the third volume.

The method of classification used in this volume is according to the types concerned, hydrocarbons are considered as one family, alcohols and phenols are discussed as members of the large family of hydroxyl compounds. Some exceptions to this method of subdivision have been made in cases where a number of substances of very diverse chemical types have a strong secondary interest which draws them into a group. Thus, in the vitamin field consideration of the many diverse structures which play so large a part in nutritional biochemistry might well have been distributed among the chapters dealing with the respective types, i.e., vitamin A to the unsaturated alcohols, vitamin B_1 to the thiazoles, B_2 to the azines, etc. It was decided to group such substances together in Chapters IX to XI.

No apology is made for the emphasis which, in this work, has been laid on the industrial applications of organic compounds, since it is felt that the Victorian hard and fast distinction between ' pure ' and ' applied ' science has disappeared, insofar as organic chemistry is concerned. Fundamental research is carried out in industrial laboratories in increasingly large measure, and the links between the University or Technical College laboratories and industry are much stronger than heretofore. The truth of the matter is that in the latter part of the nineteenth and the first decade of the present century the ' lag ' between academic research on this subject and its applications was enough to segregate ' pure ' from ' applied ' chemistry. This lag has now almost disappeared, and although the industrial laboratory distinguishes between ' long-term ' and ' short-term ' research, the older line of demarcation has nearly disappeared.

THE LITERATURE OF ORGANIC CHEMISTRY

> " Nothing will ever be attempted if all possible objections must first be overcome ".
>
> —SAMUEL JOHNSON.

It has already been mentioned that the reader of this book will be presumed to have an elementary knowledge of organic chemistry. This book will give him a working acquaintance with most of the types, reactions, properties and special topics of organic chemistry ; for further information on any topic of organic chemistry recourse must be taken to the literature of the subject.

The literature of chemistry may be divided into the following groups :—

(1) Text-books.
(2) Monographs.
(3) Scientific journals.
(4) Technical journals, which may be, in turn, subdivided into (*a*) permanent, and (*b*) ephemeral.
(5) Dictionaries and compendia, such as those of Beilstein and Richter.

Text-books of organic chemistry are compiled (by men somewhat resembling Dr. Johnson's lexicographer !) for the instruction of students. Elementary text-books introduce the subject ; intermediate works carry the reader further into it ; and from advanced text-books the student may obtain a more extensive grasp of the topics and subdivisions of the subject. In no case does a text-book give a *complete* account of any one aspect of the subject, the most that can be done in the available space is to indicate, by frequent references, the main contributions which have been made.

Monographs on more important subjects have been published in profusion ; in most cases they are a fairly complete record of the knowledge available up to their publication date, and many of general interest are referred to in this text. The monographs may be sub-divided into three classes :—

(*a*) Individual monographs, e.g., Cohn's 'Carbazol', Staudinger's 'Die Keten', or Friedmann's 'Sterols and related compounds'.

(*b*) The American Chemical Society's monograph series in which many topics of organic chemistry are exhaustively dealt with in excellently documented summaries. Examples are "The Chemistry of Natural Products related to Phenanthrene" (Fieser), A.C.S. Monograph No. 70, and "Organic Compounds of Mercury" (Whitmore).

A specialised type of monograph is the annual publication of "Organic Syntheses", now in its twenty-fifth year. This had its origin in a short series of volumes published by the University of Illinois, each containing tested directions for the preparation of a variety of organic compounds; the idea proved so attractive that it was adopted on an international basis, and a volume is produced each year. Collective volumes containing the issues I to X and XI to XX are now available. An organic chemist wishing to prepare quantities of a substance, usually turns first to "Organic Syntheses" before going to the original literature.

(*c*) A valuable series of monographs is that contained in "Chemical Reviews", an American publication of great merit, in which about fifteen to twenty subjects are treated annually in four or five issues. Most of the monographs are historically complete and are documented. A similar and equally valuable series is that just commenced by The Chemical Society as its "Quarterly Reviews".

It may be emphasised that the monograph is not often used for the communication of original work, and is not necessarily complete, although most authors endeavour to cover the whole subject; it is, in essence, a summary of work done on a particular topic, and of the relevant theories; it usually reflects the views of the author. The question of completeness is a vexed one, and may be illustrated by consideration of a subject such as methylene blue. This might well be treated chemically as part of a monograph on thiazonium compounds, and whilst a monograph could be written dealing exhaustively with the chemical problems relating to the structure, synthesis and properties of this class of compound, it might fail entirely to deal with

(*a*) Methylene blue as a bacteriological indicator;
(*b*) Methylene blue as a dyestuff; or
(*c*) Methylene blue as a bactericide in medicine;

these topics being outside the field of the author's concern.

Purely scientific journals are published regularly by various learned societies for two purposes, (*a*) the dissemination of new knowledge (original communications), and (*b*) the cataloguing and summarising of contemporary publications (abstracts).

Dealing first with original communications, we may take our own *Journal* of the Chemical Society and that of the American Chemical Society as examples. The purpose of such journals is to serve as a medium for recording new knowledge. A chemist who has discovered new facts, publishes them in such a journal that his colleagues may have knowledge of his discoveries. In such communications the full experimental details must be recorded in such a way that any competent chemist, familiar with the field, can repeat the work. Owing to the great cost of publication, authors of original papers must prune their descriptions and theoretical observations to a minimum, must strictly adhere to systematic nomenclature and many other conventions and abbreviations. This makes the style of modern journals devoted to original communications very terse and condensed, calling for very close attention in reading; forty years ago W. H. Perkin described a new compound as "a substance of singular beauty, separating from alcohol in long, pale yellow glistening prisms, often reaching a length of several inches. On heating, the substance began to decompose at 224° C." In modern journals this would become " yellow prisms, from alcohol, decomp. 224° ". The consequence is that owing to the degree of compression used there is practically no trace of any characteristic style, and many original papers tend to become a somewhat bleak, even if valuable, record of experimental facts and conclusions drawn therefrom.[1]

In this country, the publication of original chemical work has taken place mainly in the *Journal* of the Chemical Society, but the broadening of interest in biochemical and allied fields has not only led to the use of other journals, but has even stimulated the publication of additional journals. Thus, the *Proceedings and Transactions* of the Royal Society often contain important papers on chemical topics with a biological trend, whilst the *Biochemical Journal* has been founded to publish original biochemical research. Again, it was felt that the *Journal* of the Chemical Society was inappropriate for the publication of research dealing with applied chemistry, and a separate Society of Chemical Industry was formed with its own journal to deal with industrial chemistry.

It is to be regretted that in this country we have no journals comparable with the *Annalen* and *Journal für Praktische Chemie*, in which lengthy and detailed papers can be published without undue condensation.

As each country has its own set of scientific journals devoted to original records, the aggregate is very formidable, and whilst it was possible for the late Professor H. E. Armstrong, towards the end of last century, to claim truthfully that he read systematically the whole of current chemical literature (and to have read nearly all that had preceded it) it would now be impossible for any one person to read all the journals. This has led to a more active development of abstracting, a system by which a short précis of each original communication is prepared and published in classified groups.

The earliest Abstracts were the *Pharmaceutisches Zentralblatt* issued first in 1830, but in 1850 changed in title to *Chemisches und Pharmaceutisches Zentralblatt*, becoming in 1856 the *Chemisches Zentralblatt*, by which name it has been known since. It is, or was, a weekly paper.

The British system of abstracts dates from 1849, when the Chemical Society commenced the publication of abstracts. A further system of abstracts of the *Journal* of the Society of Chemical Industry was commenced in 1882. It deals almost exclusively with topics of industrial interest. In order to avoid duplication of abstracting and publication, both sets of chemical abstracts—those of the Chemical Society and of the Society of Chemical Industry—are now administered by a joint Bureau, which issues them as *British Abstracts* in seven sections :—

A. I.	General, Physical and Inorganic Chemistry.
A. II.	Organic Chemistry.
A. III.	Physiology and Biochemistry (including Anatomy).
B. I.	Chemical Engineering and Industrial Inorganic Chemistry, including Metallurgy.
B. II.	Industrial Organic Chemistry.
B. III.	Agriculture, Foods, Sanitation, etc.
C.	Analysis and Apparatus.

The American Chemical Abstracts were commenced in 1907, and are now issued fortnightly (British Chemical Abstracts are issued monthly). Prior to 1907 there was no satisfactory American abstracting system, the current " Review of American Chemical Research " (1895–1906) being only of limited scope. From

---

[1] See Appendix for Abbreviations commonly used in British Chemical literature.

1907–1914 the American Chemical Abstracts left much to be desired, but they are now the most satisfactory system in the world, as they abstract practically all chemical literature. It should be noted that an 'abstract' is not intended to do more than acquaint the reader with the scope of the paper abstracted; to indicate the main conclusions, and give an outline of the methods by which they were reached. The following abstract illustrates these points:—

> "*Formation of amides from nitriles by the action of hydrogen peroxide.* L. McMaster and C. R. Noller. *J. Indian Chem. Soc.*, *12*, 652–653.—Data for optimum conditions for the Radziszewski reaction as detd. from 2–8 expts. for 13 nitriles, using 3, 6, 12 and 30 per cent. H_2O_2 in the presence or absence of EtOH are summarised. In general, the H_2O_2 was added to a weighed amt. of the nitrile and sufficient 95 per cent. alc. to effect soln. was added (cf. Murray and Cloke, *C. A.* 29, 729^5). The soln. was made alk. with 6*N* NaOH and was kept at 60° for 4 hrs. The alk. mixt. was cooled, neutralised with H_2SO_4, evapd. and extd. with $CHCl_3$ or crystd. from H_2O. Conditions for the conversion of Et, Pr, Bu, *iso*-Bu, $PhCH_2$, Ph_2CH, $CH_2:CPh$, *o*-$O_2NC_6H_4$, *p*-$O_2NC_6H_4$, *o*-MeC_6H_4, *m*-MeC_6H_4, $(CH_2O_2)C_6H_3CH_2$ and *o*-$O_2N(CH_2O_2)C_6H_2CH_2$ nitriles into 49·6, 64·9, 62·5, 56·5, 59·5, 69·0, 83·0, 80·4, 91·2, 93·0, 84·8, 97·4 and 85·4 per cent. yields of the corresponding amides, m. 80–81°, 114·6°, 104·1°, 135·4°, 159°, 166·5°, 202–206°, 176·5°, 201·6°, 141·5°, 93·8°, 168·6° and 199·6° (all m.ps. corr.), are given (cf. *Org. Synthesis*, XIII, 94). H_2O_2 in concns. up to 30 per cent. has no effect on neutral solns. of EtCN or *o*-$O_2NC_6H_4CN$ at temps. up to 100° when decomposed catalytically by MnO_2, $Co(OH)_3$ Co_2O_3 or Ni_2O_3. The OH ion is evidently necessary as a catalyst in this reaction."
>
> —*Am. Chem. Abstr.*, 1936, **30,** 1736.

In this abstract, the method is given, with yields and melting points of the products obtained; references to several related communications are also given.

Indexes.—In the American series three indexes are published each year: an Author Index, a Subject Index, and a Formula Index. The latter contains the formulæ of all definite substances mentioned, in alphabetical order. The arrangement of all symbols within the formula is alphabetical, except in the case of carbon compounds, where C always comes first, followed immediately by H if present. Details of the method of arrangement will be found on page 9936 of Vol. 30 (1936) of "Chemical Abstracts". This volume of abstracts also contains a complete list of the journals abstracted (2808 in number).

In order to eliminate the labour of searching through many indexes, collective Decennial Indexes were published in 1916, 1926, 1936 and 1946, in which the entries of the ten-year period are arranged together. The British Abstracts have similar indexes, save that more recently Quinquennial Indexes have been adopted to bridge the gap. The collective indexes of the three abstracting systems are shown in the table below:—

British Chemical Abstracts.	American Chemical Abstracts.	Chemisches Zentralblatt.
1841–1872	—	1870–1881
1873–1882	—	—
1883–1892	—	—
1893–1902	—	1897–1901
1903–1912	1907–1916	1902–1906
1913–1922	1917–1926	1907–1911
1923–1932	1927–1936	1912–1916
1933–1937	1937–1946	1917–1921
—	—	1922–1926
—	—	1927–1931
—	—	1932–1936

Technical journals are subdivided into two classes, the permanent which have a lasting value, and the ephemeral, the interest of which is mainly topical. Thus, the *Journal* of the Society of Chemical Industry already referred to is a 'permanent' technical journal; there are many other journals of a similar, but more specialised nature, examples are:—

1. *The Analyst*.—A monthly dealing with original communications concerning analytical problems. It also comprises a specialised abstract section.
2. *Journal of the Society of Dyers and Colourists*.—A monthly dealing with topics related to the manufacture and use of dyes. It also has an independent abstract section.
3. *Industrial and Engineering Chemistry*.—Published by the American Chemical Society in three sections:—
    - (*a*) News Edition. An ephemeral publication dealing with personal notes and news.
    - (*b*) An Industrial Edition, dealing with the communication of original work of technical character. A unique publication in many ways, and of the highest value.
    - (*c*) An Analytical Edition, a medium for original communications on analytical chemistry.
4. *The Journal of Organic Chemistry*.—Published under the auspices of the American Chemical Society for the more extensive type of original communications on organic chemistry, usually with documented and historical introduction; an American analogue of the famous *Annalen* of Liebig.
5. *Journal of the Faraday Society*.—For the publication of original work on physical chemistry, and its applications.
6. *The Industrial Chemist*.—A monthly paper dealing with topics of industrial interest, many of which are of permanent value.
7. *International Tin Research, etc., Bulletin*.—Included in this list as an example of a technical publication published by an industrial research organisation. Its contents are often reprints from other journals, but occasional original communications are included.

In addition to the journals mentioned, there are many technical journals relating to branches of applied chemistry, such as rubber (*Rubber Chemistry and Technology*), petroleum (*Journal of the Institute of Petroleum*), metallurgical chemistry (*Journals of the Institute of Metals and of the Iron and Steel Institute*) in all of which original work may be published. Further, there are numerous journals devoted to pharmaceutical matters, although little of permanent value is recorded, save in the *Quarterly Journal of Pharmacy*. Most of the journals referred to in the preceding paragraph have an independent abstracting system dealing only with those items likely to be of interest in their limited sphere.

EPHEMERAL JOURNALS

General chemical day-to-day topics are dealt with by a variety of weekly and monthly papers, some of which, such as *Chemistry and Industry* and *The Industrial Chemist* have matter of more than ephemeral interest. Each subdivision of applied chemistry has its own 'trade' papers, such as *Soap*, *The Cosmetic Industry*, *The Perfumery and Essential Oil Record*, *Flavours*, *The Manufacturing Chemist*, *The Chemist and Druggist*, *Steel*, *The Citrus Industry*, *Oil and Colour Trades Journal*, and many others. The use of 'ephemeral' in respect of such journals is no implication that they are without value (the *Times* is an ephemeral publication!); the trade papers are valuable for the dissemination of news, for the publication of personal views, discussion of topics of professional interest and a good chemist makes considerable use of them for keeping his knowledge up to date; even with careful revision, new methods take many years to get into the text-books, and the excellent summaries published in such papers as *Chemistry and Industry*, the *Industrial Chemist*, *The Chemical Trade Journal*, and *The Chemical Age* are recommended to the attention of students.

It is difficult to assign a class to publications such as *Nature*, a weekly journal devoted to the publication of news and reviews of progress in all branches of natural science, a paper which has become the accepted medium of announcing discoveries of note, pending more extended (and much slower) publication in the usual channels. Such a journal is of more than usual value, and can be regarded by the student as a *sine qua non* of his current reading. From it he will learn not only what is taking place of note in his own branch of science, but also will gain the broadening effect of learning the trend of progress in other sciences. An American counterpart of *Nature* is called *Science*.

JOURNALS IN LANGUAGES OTHER THAN ENGLISH

Each country publishes a group of papers similar in scope and character to those mentioned, which have been so far either British or American. The German literature of chemistry is extensive, and contains in the *Annalen* (Liebig's *Annalen der Chemie und Pharmacie*) one of the earliest journals devoted entirely to chemistry. It has been published regularly since 1832, and many historic papers are recorded in its pages; of later years it has been devoted solely to organic chemistry, the editors encouraging the publication of comprehensive historical summaries leading up to new work. Since 1868 the German chemical journal corresponding to our *J.C.S.* or *J.A.C.S.* has been the *Berichte der Deutschen Chemischen Gesellschaft*, usually spoken of as 'the *Berichte*' or written as *Ber.*; many notable communications have been made in its pages, and it is an essential part of a chemical library. The *Journal für Praktische Chemie*, which commenced publication two years after the *Annalen* was, in some senses, a rival of the latter journal, and although it was never quite so popular, contains much data of importance. German scientists were among the first to publish specialised journals devoted to separate branches of pure chemistry. Thus, the *Zeitschrift für anorganische chemie*, the *Zeitschrift für Electrochemie*, *Zeitschrift für Krystallographie* and *Zeitschrift für Physikalische Chemie*, all of which commenced publication towards the end of last century, are each devoted to the chemical topic indicated in the title. There is also a wide range of journals in German dealing with technical subjects.

The most notable foreign journals (in addition to those already described) are :—

	Date of Commencement.	Country.
Helvetica Chimica Acta	1918	Switzerland
Annales de Chimie et de Physique. (As *Annales de Chimie*	1790–1815	France
became *Annales de Chimie et de Physique*	1816–1913	
onwards became two separate journals—*Annales de Chimie* and *Annales de Physique*)	1914	
Bulletin de la Société chimique de France	1859	France
Bulletin de la Société chimique de Belgique	1887	Belgium
Recueil des Travaux Chimiques des Pays-Bas	1882	Holland
Anales de la Sociedad Española Fisica y Quimica	1903	Spain
Gazzetta Chimica Italiana	1871	Italy
Journal of the Russian Physical Chemical Society	1869–1930	Pre-Revolution Russia
Zhurnal Oboshcheĭ Khimii	1930	Soviet Russia
Zhurnal Fizicheskoĭ Khimii	1930	Soviet Russia

Dictionaries and Special Publications

Up to the commencement of this century there had been many attempts to write complete "Treatises" on the subject of organic chemistry. Berzelius, in 1803–1818, wrote a treatise, and although he had been preceded by Bergman and many others, it is convenient to consider his treatise as the father of more modern works. When Berzelius died Gerhardt wrote (in 1853) his "Traité de chimie organique", which is really a re-written form of the last French edition of Berzelius' treatise. It is a pleasant readable summary of the knowledge available at that time, and may still be read with interest by the serious student of organic chemistry. It contains collected data on many unusual substances, some of which have been lost sight of in more recent times. The works of Berzelius and Gerhardt laid the foundations on which later authors, including Gmelin, Beilstein and Richter, built. Attention may be directed to the monumental "Traité de Chimie Organique" conceived and edited by V. Grignard; the work was projected in twenty volumes, of which fourteen had been published by 1945. The work is not a dictionary or reference work in the ordinary sense, but preserves the spirit of Gerhardt's "Traité", and provides a readable and detailed study of the main topics of organic chemistry.

In this country, one of the earliest works of reference on organic chemistry was George Fownes' "Manual", published in 1847. Fownes was one of the earliest Professors of practical chemistry at University College, London, and published this work for the use of students. It proved a valuable and popular book, and was faithfully re-edited and kept up-to-date after the death of the author by first H. Bence-Jones, A. W. Hofmann, and later by Henry Watts, who carried it through to the twelfth edition, published in 1877. Meanwhile, Watts had realised the need for a more comprehensive work covering as far as possible, all existing knowledge, and in 1863 there appeared his "Dictionary of Chemistry and the Allied Branches of other Sciences". The work proved immediately successful, and Watts carried it, with the aid of three periodical supplements, to a second edition in 1872. After his death the dictionary was replaced by two complementary publications, one (issued in 1888) edited by H. Foster Morley and M. M. Pattison Muir, under the title, "Watts' Dictionary of Chemistry, Revised and entirely Rewritten", and dealing with Chemistry only; the other (issued in 1890) edited by Edward Thorpe, under the title, "Thorpe's Dictionary of Applied Chemistry", dealing with the application of Chemistry to the Arts and Manufactures. Thorpe carried his dictionary through three editions. The third edition, completed in 1925, was brought up to date by the publication of a supplement (1934–1936) under the editorship of J. F. Thorpe and M. A. Whiteley, who also produced the first six volumes of the present fourth edition (1937–1943), the completion of which is now in the hands of an Editorial Board, under the chairmanship of I. M. Heilbron. Thus from 1890 the editorial work of "Thorpe's Dictionary of Applied Chemistry" has been carried on without a break by the professorial staff of the Royal College of Science, Imperial College of Science and Technology, London.

The rapid growth of chemical science in modern times, particularly in Physical Chemistry and its application to industry, has called for some change in the scope of the Dictionary and, under the direction of the Editorial Board, a greater proportion of articles on Physical Chemistry is included in the present edition.

Meanwhile, in 1877, Roscoe and Schorlemmer started the publication of their "Treatise on Chemistry" with Vol. I, "The Non-metals", followed in 1878 by "The Metals". Vol. III was to deal with organic chemistry, and was projected in about seven or more parts, six of which were issued between 1881–1892, when Schorlemmer died, and the remainder of the work was not published as originally projected, but was continued in the German edition by

J. W. Brühl of Heidelberg, with the publication of the " Fünfgliedrige heterocyklischen System " published in 1898. By this time chemistry, especially the organic division, was advancing too rapidly for one single man, or any small group of men, to hope to cover all the ground in a general descriptive and detailed fashion, although the need for a comprehensive reference work was becoming more acute.

The earlier efforts of L. Gmelin had resulted in the publication in 1819 of a " Handbüch der Organischen Chemie ", during the revision of the fourth edition of which, in 1853, Gmelin died ; his " Handbuch " must be considered a progenitor of " Beilstein ". Beilstein commenced the collection of data about 1860, mainly for his own convenience in research, and only later conceived the idea of publication. During 1880–1882 the first edition of " Beilstein " appeared. Beilstein produced a second edition (1886–1890) and, of the third, 1892–1899, he prepared the main volumes, but in 1895, realising that the task of continuing the " Handbüch " was too much for a single individual, he transferred his rights to the German Chemical Society, whose first task was the preparation of the four supplementary volumes and index, to the third edition. This task was completed by 1906 under the editorial supervision of Jacobson. Since that date the ' new ' edition has been prepared, of late years, under the editorship of F. Richter, as a special activity of the German Chemical Society.

The purpose of Beilstein's " Handbüch der Organischen Chemie " was to catalogue systematically all known organic substances, with their physical properties, chemical reactions and preparation, and to furnish references to original literature. This book, and its subsequent editions, has become the chief reference work of the organic chemist, but Beilstein's original method of classification has been altered. That this would become necessary was recognised by the original author, and during 1907 Jacobson and Prager developed the new system which was published in one hundred and thirty-three pages ; the old material of the 1906 edition was rearranged according to the new system (1908–1912), and the modern edition of Beilstein commenced publication in 1918 with Vol. I, and continued until Vol. XXVII was published in 1937. Vol. XXVIII (in two parts) is the Index, and Vol. XXIX is the Formula Index (a feature which was missing in the original edition and was supplied by Richter's " Lexikon der Kohlenstoff-Verbindungen "). The literature up to January 1, 1910, is covered in the first set of twenty-seven volumes, and that from 1910–1919 by a second set of volumes, each supplementary to one of the first series. A second supplement covering from 1920–1929 has been commenced, but does not appear likely to be completed until 1950. A new, photolithographically reproduced, reprint of this edition of Beilstein has been produced in America by Edwards Brothers, Inc., which has made this valuable work more readily available, and at approximately one-third of the original cost, which was about £250.

PATENT LITERATURE

Since data on organic chemical topics has been accumulated in industrial research, it is mentioned in the Patent Literature, often without reference elsewhere. This may necessitate a search in the Patent Office Abridgements, which, although aided by the Quinquennial Indexes and the fifty year Collective Index, 1860–1910, is still a difficult matter, as all entries in the Abridgements are made numerically. If the abridgement indicates that the patent is of interest, it is a simple matter to obtain the full specification. Since 1920, the American Abstracts have fully covered chemical patents, and a special search is not usually necessary.

It may not be out of place to advise students not to place too much reliance on information abstracted from Patent specifications, which are occasionally deliberately made misleading (*a*) by claiming more widely than is justified by actual experimental evidence, and (*b*) by focussing attention on methods known to give poor results. Thus, if a reaction is found to be satisfactory with aniline, *o*- and *p*-toluidine as starting points, a claim may be made covering the use of all arylamines. The argument used is that the reaction is one which appears to be applicable to all simple arylamines, and therefore as it has been shown experimentally to proceed for some of them, the claim may legitimately be extended to them all. Since the final specification for the Patent does not disclose which amines have been tried and which not, the student should avoid placing too much reliance on ubiquity. In the second case (*b*), attention is focussed on a method which, although workable, is not the best method ; thus a patent may describe in detail an example in which a condensation is effected in ' solutions of caustic alkalies ', and the example may describe the use of caustic soda of 10 per cent. strength ; the solution actually used industrially may be a 5 per cent. solution of caustic potash. The latter is an ' obvious chemical equivalent ', and as such is protected by the Patent.

Foreign patents not registered in Great Britain cannot be searched for in the Abridgements, but much valuable data concerning them is contained in the following :—

(1) Friedländer—' Fortschritte in der Teerfarbenfabrikation u.s.w.', commencing in 1877 and continuing until 1921, a series of thirteen volumes dealing with *every* German specification on organic chemistry since 1877.
(2) Lange—' Die Zwischenprodukte der Teerfarbenfabrikation ', 1920. A systematic reference book of aromatic intermediates.
(3) Winther—' Patenten der organischen Chemie ', 1877–1905. A useful book (3 vols.) for earlier work.

Making a literature search may be a lengthy or short operation according to the purpose and nature of the search. If simple physical properties are sought, Seidell's " Solubilities " (first published in 1907, but re-issued in a new form in 1919, with a supplement in 1928) may give preliminary data ; for melting or boiling point it is usually worth while trying Richter's " Lexikon " or Heilbron's " Dictionary of Organic Compounds " ; better known substances may be described from the physicochemical standpoint in Landolt and Börnstein's " Physikalische-Chemische Tabellen " (1923).

In organic chemical research it is frequently necessary to search for details concerning the preparation of a substance to be used as a starting point. " Organic Syntheses " is usually consulted first, whilst the following reference works often contain full preparative details.

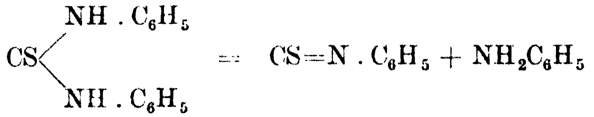
1. Vanino—" Handbuch der praparative Chemie " (2 vols.).
2. Houben-Weyl—" Die Methoden der organischen Chemie " (4 vols.).
3. Lassar-Cohn—" Handbuch der Arbeitsmethoden der organischen Chemie " (2 vols.).
4. Abderhalden—" Biochemische Arbeitsmethoden ".

Useful information can still be extracted from Part III in six volumes of Roscoe and Schorlemmer's " Treatise ", and Heilbron's " Dictionary " frequently has a literature reference to a good method of preparation. Unless, however, the scope of the enquiry is very limited and the searcher has a shrewd idea as to where the required information is to be found, it is better to make a systematic search. As an example of the method used and of the results to be expected, the substance " phenyl mustard oil " has been chosen, empirical formula C_7H_5NS. Little concerning the compound can be found in the ordinary textbooks ; thus, in Whitmore's " Organic Chemistry " (1937) the entry is

" *Thiocarbanilide*, diphenylthiourea $(PhNH)_2CS$, m. 154°, a derivative of thiocarbonic acid, is readily made by boiling aniline with CS_2. With HCl it gives *phenyl mustard oil*, phenyl isothiocyanate, PhNCS, b. 222°. This gives mixed thioureas with primary and secondary amines ".

In Roscoe and Schorlemmer more detail is given up to the date of publication, 1886, thus (Vol. III, Part III, p. 221) :—

" Phenyl thiocarbimide or phenyl mustard oil, $C_6H_5 . N{=}CS$.—Hofmann obtained this body by the distillation of diphenyl thiocarbamide (sulphocarbanilide) with phosphorus pentoxide and named it sulphocarbanil or phenyl sulphocyanide.[1] It may be more simply obtained by heating the thiocarbamide with concentrated hydrochloric acid.[2]



$$CS\begin{cases} NH . C_6H_5 \\ NH . C_6H_5 \end{cases} = CS{=}N . C_6H_5 + NH_2C_6H_5$$

It is also formed by the action of thiocarbonyl chloride, $CSCl_2$, on aniline,[3] as well as by the direct combination of sulphur with phenyl carbamine,[4] and when phenyl isocyanate is heated with phosphorus pentasulphide.[5]

" It is a liquid with a smell similar to that of ordinary mustard oil, boils at 222°, and combines with ammonia and the amines to form thioureas. It also combines with alcohol to form ethers of thiocarbanilic acid (p. 224).

" When chlorine is passed through its solution in chloroform, isocyanophenyl chloride, $C_6H_5 . N = CCl_2$, is obtained as a heavy yellow, pungent liquid, boiling at 211–212°. It possesses a very unpleasant pungent odour, and its vapour attacks the eyes and mucous membrane. Dry silver oxide acts on it violently with partial carbonisation and formation of phenylcarbimide." [6]

The entry in Heilbron's " Dictionary " (1937) is :—

" PHENYLISOTHIOCYANATE

$C_6H_5 . N : CS$

C_7H_5NS M.W. 135

" Colourless liquid, F.P. —21°. B.p. 221°, 131·8°/63 mm., 120–121°/35 mm., 95°/12 mm. D_4^4 1·1477, D_4^{25} 1·1288, D_4^{35} 1·1202, D_4^{50} 1·1061, $n_D^{23 \cdot 4}$ 1·64918. Heat of combustion Cv. 1019·0 Cal., Cp. 1020·3 Cal."

Dains, Brewster, Olander, " Organic Syntheses ", Collective Vol. I, 437 give the following details of preparation :—

" PHENYL ISOTHIOCYANATE

$$C_6H_5NH_2 + CS_2 + NH_4OH \longrightarrow C_6H_5NHCS_2NH_4 + H_2O$$

$$C_6H_5NHCS_2NH_4 + Pb(NO_3)_2 \longrightarrow C_6H_5NCS + NH_4NO_3 + HNO_3 + PbS$$

‘ 1. *Procedure.*

" In a 500-cc. round-bottomed flask (Note 1), fitted with a mechanical stirrer and surrounded by an ice-salt cooling bath, are placed 54 g.

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[1] Hofmann, *Jahresb.*, 1858, 349.

[2] Merz and Weith, *Zeitschr. Chem.*, 1869, 589.

[3] Rathke, *B.*, 3, 861.

[4] Weith, *ibid.*, 6, 211.

[5] Michael and Palmer, *Amer. Chem. Journ.*, 6, 257.

[6] Sell and Zierold, *Ber.*, 7, 1228.

(43 c.c., 0·71 mole.) of carbon disulfide and 90 c.c. (1·3 moles.) of concentrated aqueous ammonia (sp. gr. 0·9). The stirrer is started and 56 g. (0·6 mole.) of aniline (Note 2) is run into the mixture from a separatory funnel at such a rate that the addition is complete in about twenty minutes. The stirring is continued for thirty minutes after all aniline has been added, and then the reaction mixture is allowed to stand for another thirty minutes. During this time a heavy precipitate of ammonium phenyldithiocarbamate separates, and may even stop the stirrer.

" The salt is dissolved in 800 c.c. of water (Note 3), and transferred to a 5–l round-bottomed flask. To the solution is added with constant stirring a solution of 200 g. (0·6 mole.) of lead nitrate in 400 c.c. of water. Lead sulfide separates as a heavy brown precipitate which soon turns black. The mixture is then distilled with steam into a receiver containing 5–10 c.c. of 1 *N* sulfuric acid as long as any oil comes over (Note 4). About 2–3 l. of distillate is collected. The product is separated from the water and weighs 63–66 g.

" The oil is dried over a little calcium chloride and distilled under reduced pressure. The yield of phenyl isothiocyanate boiling at 120–121°/35 mm. is 60–63 g. (74–78 per cent. of the theoretical amount. Notes 5 and 6)."

2. *Notes.*

1. If the reaction is carried out in a beaker, so much ammonia is lost by volatilisation that the crystalline ammonium phenyldithiocarbamate is not formed. The temperature should be from 0–10° to avoid loss of ammonia.
2. Ordinary technical aniline was used in these experiments.
3. The transfer of the salt to the 5–l. flask is conveniently made by the addition of four successive 200-cc. portions of water to the flask containing the salt.
4. The sulfuric acid is added to react with any ammonia that may be carried over. Otherwise the ammonia may react with the product to give phenylthiourea.
5. Larger runs give somewhat lower percentage yields ; thus 280 g. of aniline gives about 250 g. (61 per cent. of the theoretical amount) of redistilled phenyl isothiocyanate.
6. This reaction is a general method of preparation for aryl isothiocyanates in yields of 50–75 per cent. of the theoretical amount.

3. *Methods of Preparation.*

" Phenyl isothiocyanate can be prepared from thiocarbanilide by the action of phosphorus pentoxide,[1] hydrochloric acid,[2] iodine,[3] phosphoric acid,[4] acetic anhydride,[5] and dilute sulfuric acid ;[6] and from ammonium phenyldithiocarbamate by the action of ethyl chlorocarbonate,[7] copper sulfate,[8, 9] lead nitrate,[9] ferrous sulphate [9] and zinc sulfate.[9]"

Full details of the preparation are given in " Organic Syntheses ", as indicated above.

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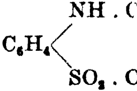
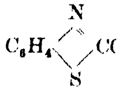
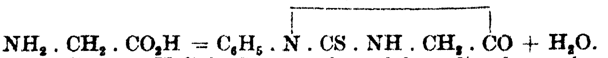
[1] Hofmann, *Jahresber.*, 1858, **349.**
[2] Weith and Merz, *Z. Chem.*, 1869, **589.**
[3] Hofmann, *Ber.*, 1869, **2,** 453 ; Rudnev, *J. Russ. Phys. Chem. Soc.*, 1878, **10,** 184.
[4] Hofmann, *Ber.*, 1882, **15,** 985.
[5] Wernor, *J. Chem. Soc.*, 1891, **59,** 396.
[6] Bly, Perkins and Lowis, *J. Am. Chem. Soc.*, 1922, **44,** 2896.
[7] Kaluza, *Monatsh.*, 1912, **33,** 367.
[8] Losanitsch, *Ber.*, 1891, **24,** 3021.
[9] Dains, Brewster and Olander, *Univ. Kansas Sci. Bull.*, 1922, **13,** 1 (*C.A.*, 1923, **17,** 543).

Richter's " Lexikon " has this entry :—

" C_7H_5NS (1) Phenylsenföl (Thiocarbanil). Sd. 222° (*B. 3*, 772, 861 ; *6*, 211 ; *9*, 1266 ; *11*, 2267 ; *12*, 1127 ; *14*, 445, 1083 ; *15*, 985 ; *19*, 568 ; *J*. 1858, 349 ; *Z*. 1869, 589 ; *Am. 6*, 258 ; *J. r. 10*, 184 ; *Soc. 59*, 327, 400, 548 ; *J. Pr.* [2], *32*, 294 ; *G. 16*, 70—II, 388."

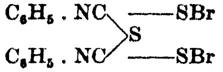
The ' II, 388 ' is the reference to Beilstein (3rd Edition) which reads as follows :—

Thiocarbanil (*Phenylsenföl*) $C_7H_5NS = C_6H_5 . N : CS$. *B*. Aus Thiocarbanilid und P_2O_5 (Hoffmann, *J*., 1858, 349). Beim Erhitzen von Thiocarbanilid mit koncentrirten Salzsäure (Weith, Merz, *Z*., 1869, 589). Aus $CSCl_2$ und Anilin (Rathke, *B*., **3**, 861). Beim Erhitzen von Phenylisocyanid mit Schwefel (Weith, *B*., **6**, 211). Beim Behandeln einer alkoholischen Lösung von Thiocarbanilid mit Jod, neben Triphenylguanidin (Hofmann, *B*., **2**, 453) und Anilin (Rudnew, *J. der russ. chem. Gesellschaft*, 10, 184). $3CS(NH \cdot C_6H_5)_2 + 2J = 2C_6H_5 . NCS + CH_2(C_6H_5)_3N_3 . HJ + C_6H_5 . NH_2 . HJ + S$. Um die Bildung von Nebenprodukten (Carbanilid u.s.w.) zu vermeiden, wendet man am besten eine Benzollösung von Thiocarbanilid an (Rudnew). Beim Erhitzen von Phenylcarbonimid oder von Phenylurethan $NH(C_6H_5) . CO_2 . C_2H_5$ mit P_2S_5 auf 160° (Michael, Palmer, *Am*., **6**, 258). — *D*. Man erhitzt 1 Thl. Thiocarbanilid mit 2–3 Thln. Phosphorsäurelösung (spec. Gew. = 1·7) ½ Stunde lang, bis das Schäumen aufhört (Hofmann, *B*., **15**, 986). Man kocht 5 Minuten lang 1 Thl. Thiocarbanilid mit 1 Thl. Essigsäureanhydrid (Werner, *Soc*., 59, 400).—Nach Senföl riechende Flüssigkeit. Siedep.: 222° ; spec. Gew. = 1·135 bei 15·5° (Hofmann). Siedep.: 95° bei 11·92 mm. ; 117·1° bei 32·08 mm. ; 121·0° bei 37·3 mm. ; 131·8° bei 63 mm. ; 218·5° bei 760 mm. (Kahlbaum, *Siedetemp. u. Druck*, 96). Siedep.: 219·8°, bei 748·8 mm. ; spec. Gew. = 0·9398 bei 220°/4° (R. Schiff, *B*., **19**, 568). Siedep.: 220·1° (i.D.) bei 748·3 mm. (von 0°) ; spec. Gew. = 1·12891 bei 23·4°/4° ; Molek.-Brechungsvermögen = 76·48 (Nasini, Scala, *G*., 16, 70). Kupferpulverent zeiht dem Phenylsenföle bei 200° Schwefel und erzeugt Benzonitril. Salzsäuregas, in eine Lösung von Phenylsenföl in absolutem Alkohol (oder in Isobutylalkohol) geleitet, spaltet Anilin ab (Pinner, *B*., **14**, 1083). $C_6H_5 . N : CS + H_2O = C_6H_5 . NH_2 + CSO$. Schwefelwasserstoff wirkt, schon bei gewöhnlichen Temperatur, unter Bildung von CS_2 und Thiocarbanilid (Proskauer, Sell, *B*., **9**, 1266). Zerfällt, beim Kochen mit Wasser, in CO_2, H_2S und Thiocarbanilid (Bamberger, *B*., **14**, 2642). Beim Erhitzen mit Eisessig auf 130° entstehen Acetanilid, COS, und, bei Anwesenheit von Wasser (Werner, *Soc*., **59**, 548), auch *s*-Diphenylcarbamid (Claus, Völtzkow, *B*., 14, 445– ; Gumpert, *J. pr*. [2] **32**, 294 ; Cain, Cohen, *Soc*., 59, 327). Verbindet sich mit SO_3 zu  $C_6H_4\left\langle\begin{array}{l}NH\,.\,CS\\SO_2\,.\,O\end{array}\right.$ (Magatti, *B*., 11, 2267). $OH . SO_2Cl$ erzeugt den Körper $C_7H_5NS_2O_3$, neben wenig $C_{14}H_{10}N_2S_3$(s.u.). Beim Erhitzen mit PCl_5, im Rohr, auf 100° entstehen Isocyanphenylchlorid, das Thioanhydroderivat  $C_6H_4\left\langle\begin{array}{c}N\\S\end{array}\right\rangle CCl$ und daneben PCl_3 und $PSCl_3$ (Hofmann, *B*., 12, 1127). Verbindet sich direkt mit Ammoniak, Hydroxylamin und Basen zu substituirten Thioharnstoffen. Phenylsenföl verbindet sich direkt mit Aminosäuren der Fettreihe (Glycin, Alanin), schon beim einfachen Zusammenschmelzen, zu Anhydriden von Thiocarbamidsäuren. $C_6H_5 . NC : S +$  $NH_2 . CH_2 . CO_2H = C_6H_5 . \overline{N . CS . NH . CH_2 . CO} + H_2O$. Diese Anhydride werden von alkoholischem Kali in Säuren übergeführt, die aber, schon bei gewöhnlicher Temperatur, wieder in Wasser und Anhydrid zerfallen. (Die Senföle der Fettreihe verbinden sich nicht mit jenen Aminosäuren zu analogen Körpern). Mit Aminobenzoësäure verbindet sich Phenylsenföl sehr leicht zu Phenylthiocarbaminobenzöesäure. Verbindet sich mit Hydrazin N_2H_4 zu Phenylthiosemicarbazid $C_7H_9N_3S$, resp. Hydrazindicarbonthiophenylamid $C_{14}H_{14}N_4S_2$. Alkoholisches Kali erzeugt Thiocarbanilid und dann Carbanilid. Beim Erhitzen mit Alkoholen entstehen Thiocarbanilsäureester (Hofmann, *B*., 3, 772). Liefert, mit $AlCl_3$, Phenylsenfölsulfid $(C_6H_5NCS)_2S$; mit Benzol und $AlCl_3$ entstehen Thiobenzanilid und Phenylsenfölsulfid. Mit Anisol und $AlCl_3$ entsteht Thioannissäureanilid. Aldehydammoniak und Phenylsenföl s. Anilin und Aldehyde.

Chlor, in eine Chloroformlösung von Phenylsenföl geleitet, erzeugt zunächst ein Chlorid $(C_7H_5NSCl)_2$ und dann Isocyanphenylchlorid $C_6H_5 . NCCl_2$, neben wenig *p*-Chlorisocyanphenylchlorid $C_6H_4Cl . NCCl_2$. Mit Brom entsteht, unter gleichen Verhältnissen, das Bromid $(C_7H_5NS . Br)_2$.

Chlorid $(C_7H_5NSCl)_2$. *B*., Beim Einleiten von trocknem Chlor in eine Lösung von 1 Thl. Phenylsenföl in 3 Thln. $CHCl_3$ (Helmers, *B*., 20, 786). Sowie die Lösung schwach

gelblich wird, lässt man sie stehen und wäscht den, nach einiger Zeit gebildeten, Niederschlag mit $CHCl_3$. Krystallinisch. Schmilzt unter Zersetzung bei 150–160°. Ausserst leicht zersetzlich. Wird durch Wasser oder Alkohol in HCl und Phenylsenföloxyd zerlegt. Bei der Einwirkung von H_2S, Kalilauge oder Natriumamalgam entsteht Diphenylthiocarbamid $CS(NH . C_6H_5)_2$.



Bromid $C_{14}H_{10}N_2S_3Br_2$ = $$\begin{array}{l} C_6H_5 . NC \diagdown \text{——}SBr \\ \qquad\qquad\quad > S \\ C_6H_5 . NC \diagup \text{——}SBr \end{array}$$. *B.* Aus Phenylsenföl und Brom (Proskauer, Sell, *B.*, 9, 1262). $3C_6H_5 . N : CS + 2Br = C_{14}H_{10}N_2S_3Br_2 + C_6H_5 . NC$.—Tief orange-rothe krystallinische Masse. In $CHCl_3$ sehr schwer löslich. Wird von Wasser, Alkohol und Essigsäure rasch zersetzt. Beim Kochen des Bromids mit Wasser entsteht eine *Base* $C_6H_5NO[C_{14}H_{10}N_2S_3Br_2 + 5H_2O = C_6H_5NO + C_6H_5 . NH_2 + 2HBr + 3H_2S + 2CO_2]$. Die Base krystallisirt (aus wässerigem Alkohol) in langen Nadeln. Schmelzp.: 156°. Wenig löslich in heissem Wasser, leicht in Alkohol.

Bromide $(C_7H_5NSBr)_2$. *B.* Nach Helmers (*B.*, 20, 789) entsteht beim Eintragen von 10 g. Brom., gelöst in 20 g. Eisessig, in eine Lösung von 5 g. Phenylsenföl in 10 g. Eisessig das Additionsprodukt $C_7H_5NS . Br_2$ in rothen Krystallen, das, schon an der Luft, Brom verliert und bei ½–1 stündigem Erhitzen auf 100° den Körper $(C_7H_5NSBr)_2$ hinterlässt. Dieser krystallisirt (aus heissem Eisessig) in glänzenden Blättchen, die bei 190°, unter Zersetzung, schmelzen. Wird von Alkohol in HBr und Phenylsenföloxyd zerlegt.

Oxyd $C_{14}H_{10}N_2S_2O = (C_7H_5NS)_2O$. *B.* Beim Auflösen von Phenylsenfölchlorid oder Phenylsenfölbromid in warmem Alkohol (Helmers, *B.*, 20, 787).—Gelbe Nadeln (aus Weingeist). Schmelzp.: 118°. Liefert mit H_2S Diphenylthiocarbamid $CS(NH . C_6H_5)_2$.

Verbindung $C_7H_5NS_2O_3 + H_2O = CS . N . C_6H_4 . SO_3H + H_2O$ (?). *B.* Aus Phenylsenföl und $OH . SO_2Cl$ (Pawlewski, *B.*, 22, 2201).—Dicke Tafeln (aus Wasser). Schwer löslich in kochendem Wasser, fast unlöslich in starkem Alkohol.

Phenylsenfolsulfid $C_{14}H_{10}N_2S_3 = (C_6H_5 . N : CS)_2S$. *B.* Entsteht, neben der Base C_6H_5NO, beim Kochen des Bromids $C_{14}H_{10}N_2S_3Br_2$ (s.o.) mit Alkohol oder Essigsäure (Proskauer, Sell, *B.*, 9, 1264). Entsteht, neben Thiocarbonylthiocarbanilid und salzsaurem Triphenylguanidin, beim Erwärmen von *s*-Diphenylthioharnstoff mit Benzol und $CSCl_2$ auf dem Wasserbade (Freund, Wolf, *B.*, 25, 1463). Man verdampft zur Trockne und krystallisirt den Rückstand wiederholt aus heissem absol. Alkohol um. Ensteht, neben $C_7H_5NS_2O_3$, beim Eintröpfeln von $OH . SO_2Cl$ in Phenylsenföl (Pawlewski, *B.*, 22, 2200). Beim Auskochen des Produktes mit Wasser bleibt das Sulfid $C_{14}H_{10}N_2S_3$ ungelöst. Entsteht bei ¼ stündigem Kochen von 5 g. Phenylsenföl mit 5 g. $AlCl_3$ (Friedmann, Gattermann, *B.*, 25, 3526).—Tiefgelbe Nadeln (aus absol. Alkohol). Schmelzp.: 156° (F., W.); 152° (P., S.); 154° (F., G.). Leicht löslich in CS_2 und Benzol, sehr leicht in $CHCl_3$. Schwer löslich in absol. Alkohol, leichter in Aether, in warmem Eisessig, in CS_2 und Benzol. Wird durch Kochen mit Essigsäureanhydrid oder Anilin nicht verändert. Wird durch konc. Kalilauge in CO_2, H_2S, Anilin und Phenylsenföl zerlegt.

In this extract the reader will recognise the references to original literature previously cited; and although compressed, this account of the chemistry of phenyl mustard oil is nearly complete up to the date of publication.

The latest edition of Beilstein contains in Vol. XII, and the first supplement to Vol. XII, the entries "*12.* 453 (261)", which are given verbatim below :—

‘ *Thiokohlensaure-anil*, *Thiocarbanil*, *Phenylisothiocyanat*, *Phenylsenföl* $C_7H_5NS = C_6H_5 . N : CS$.

Bildung.

Man fügt tropfenweise Anilin zu einer Lösung von Thiophosgen (*Bd.* III, 134) in Ather, bis die gelbe Farbe der Lösung verschwunden ist (Rathke, *A.* **167**, 218). Beim Erhitzen von Phenylisocyanid (*S.* 191) mit Schwefel (Weith, *B.* **6**, 211). Beim Erhitzen von Phenylisocyanat (*S.* 437) oder von Phenylurethan (*S.* 320) mit Phosphorpentasulfid auf 160° (Michael, Palmer, *Am.* **6**, 258). Neben anderen Produkten aus Phenylthioharnstoff (*S.* 388), Salzsäure und Natriumnitrit bei 3–5° (Haager, Doht, *M.* 27, 277). Aus Thiocarbanilid (*S.* 394) durch Einw. von Phosphorpentoxyd (A. W. Hofmann, *J.* 1858, 340) oder von sirupöser Phosphorsäure, von Chlorwasserstoff (A. W. Hof., *J.* 1858, 349; *B.* **15**, 985), konz. Salzsäure (Merz, Weith, *Z.* 1869, 589), rauchender Salzsäure (Weith, *B.* **6**, 210) oder siedendem Essigsäureanhydrid (Werner, *Soc.* **59**, 399, 400; vgl. Hugershoff, *B.* **32**, 3649). Aus Thiocarbanilid beim Erwärmen mit Acetylchlorid auf 50° (neben Acetanilid und geringen Mengen N . N′-Diphenyl-acetamidin, *S.* 248) oder beim Erhitzen mit Benzoylchlorid auf 150° (neben Benzanilid und Spuren von N . N′-Diphenyl-benzamidin, *S.* 273) (Dains, *Am. Soc.* **22**, 192). Neben N . N′ . N″-Triphenyl-guanidin (*S.* 451) (A. W. Hof., *B.* **2**, 453) und Anilin (Rudnew, *J. der russ. chem. Gesellschaft*, **10**, 184; *B.* **11**, 987) beim Behandeln einer siedenden alkoholischen (A. W. Hof., *B.* **2**, 453) oder besser, um die Bildung von Nebenprodukten zu vermeiden, einer benzolischen (Rud.) Lösung von Thiocarbanilid mit Jod. Beim Erhitzen von 1 Mol.-Gew. Thiocarbanilid mit 1 Mol.-Gew.

Phenylisocyanat in Gegenwart von Benzol im geschlossenen Rohr auf 180°, neben Carbanilid (Goldschmidt, Meissler, *B.* **27,** 272). Beim Erhitzen von Carbodiphenylimid (*S.* 449) mit CS_2 im geschlossenen Rohr auf 140–150° (Weith, *B.* **7,** 1308). Neben N . N′ . N″-Triphenylguanidin, aus Carbodiphenylimid und Thiocarbanilid durch mehrstündiges Erhitzen im Ölbade auf 150° oder besser durch kurzes Erwärmen der Benzollösung auf dem Wasserbade in Gegenwart von alkoh. Salzsäure oder Jodwasserstoffsäure (Weith, *B.* **9,** 810, 813). Beim Erhitzen von S-Methyl-N . N′-diphenyl-isothioharnstoff (*S.* 460) mit Schwefelkohlenstoff im geschlossenen Rohr auf 160°, neben Dithiocarbanilsäuremethylester (*S.* 415) (Will, *B.* **15,** 342). Neben Dimethyldisulfid (*Bd.* I, *S.* 291) beim Erhitzen von S . S′-Dimethyl-N . N′-diphenyl-isothiuramdisulfid (*S.* 464) im geschlossenen Rohr auf 100–130° (v. Braun, *B.* **36,** 2264). Beim Erhitzen von N . N′-Diphenyl-benzamidin (*S.* 273) mit CS_2 im geschlossenen Rohr auf 130–140°, neben Thiobenzanilid (Bernthsen, *A.* **192,** 34).

Darstellung.

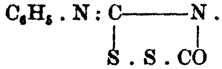
Man erhitzt 30 g. Thiocarbanilid mit 120 g. konz. Salzsäure am absteigenden Kühler, bis ca. 20 ccm. Flussigkeit zurückgeblieben sind (Gattermann, *Die Praxis des organischen Chemikers,* **12,** Aufl. (Leipzig, 1914), *S.* 218).

Physikalische Eigenschaften.

Farblose, nach Senföl riechende Flüssigkeit (A. W. Hofmann, *J.* 1858, 349). F:-21° (korr.) (v. Schneider, *Ph. Ch.* **22,** 234). Kp_{762}: 222° (A. W. Hof., *J.* 1858, 349; *C.r.* **47,** 423); Kp_{760}: 221° (korr.) (Perkin, *Soc.* **69,** 1204), 218·5° (Kahlbaum, Siedetemperatur und Druck in ihren Wechselbeziehungen (Leipzig, 1885), *S.* 96); $Kp_{748\cdot8}$: 219·8° (R. Schiff, *B.* **19,** 568); $Kp_{748\cdot3}$: 220·1° (korr.) (Nasini, Scala, *G.* **17,** 69, 70; *R. A. L.* [4] **2,** 620); $Kp_{720\cdot4}$: 219° bis 219·2° (Bolle, Guye, *C.* 1905, *I,* 868); Kp_{63}: 131·8°; $Kp_{37\cdot3}$: 121·0°; $Kp_{32\cdot08}$: 117·1°; $Kp_{11\cdot92}$; 95° (Kahl, Siedetemperatur und Druck, *S.* 96). Mit Wasser unzersetzt destillierbar (A. W. Hof., *J.* 1858, 349; *C.r.* **47,** 424). D'_4: 1·1503; D_4^{25}: 1·1278 (Walden, *Ph. Ch.* **55,** 228); D_4^4: 1·1477 (Per., *Soc.* **69,** 1204); $D_4^{23.4}$: 1·12891 (Na., Sca.); D_4^{230}: 0·9398 (R. Schiff, *B.* **19,** 568); D_{15}^{15}: 1·1382; D^{25}_{25}: 1.1314 (Per., *Soc.* **69,** 1204). $D^{13.2}$: 1·1400; $D^{38.8}$: 1·1148; $D^{54.8}$: 1·1000; $D^{78.6}$: 1·0781; $D^{109.2}$: 1·0493; $D^{152.2}$: 1·0083 (Bolle, Guye, *C.* 1905, *I,* 868, 869). $n\alpha^{23.4}$: 1·63959; $n_D^{23.4}$: 1·64918; $n\gamma^{23.4}$: 1·69938 (Na. Sca., *G.* **17,** 70). Molekulare Oberflächenspannung: Bolle, Guye, *C.* 1905, *I,* 868. Oberflächenspannung und Binnendruck: Walden, *Ph. Ch.* **66,** 393. Innere Reibung bei 0° und 25°: Wal., *Ph. Ch.* **55,** 228. Molekulare Verbrennungswärme bei konstantem Volumen: 1019·0 Cal., bei konstantem Druck: 1020·3 Cal. (Berthelot, *C.r.* **130,** 445). Magnetisches Drehungsvermögen: Per., *Soc.* **69,** 1244. Dielektr.-Konst.: Wal., *Ph. Ch.,* **46,** 179; Eggers, *C.* 1904, *I,* 1390. Elektrisches Leitvermögen: Wal., *Ph. Ch.,* **46,** 179.

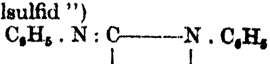
Chemisches Verhalten.

Einwirkung anorganischer Reagenzien. Phenylsenföl gibt beim Kochen mit viel überschüssigem Kupferpulver unter intermediärer Bildung von Phenylisocyanid (*S.* 191) Benzonitril (Weith, *B.* **6,** 212). Phenylsenföl wird von Aluminiumamalgam in Äther zu Thiocarbanilid und Methylmercaptan reduziert (Gutbier, *B.* **34,** 2034). Schwefelwasserstoff wirkt auf Phenylsenföl bei gewöhnlicher Temperatur unter Bildung von CS_2 und Thiocarbanilid ein (Proskauer, Sell, *B.* **9,** 1266). Leitet man Chlor in eine Lösung von Phenylsenföl in Chloroform bis zur Sättigung ein, so erhält man Phenylisocyanid-dichlorid $C_6H_5 . N : CCl_2$ (*S.* 447) (Sell, Zierold, *B.* **7,** 1228; Nef, *A.* **270,** 284). Bei der Einw. von Chlor auf überschüssiges Phenylsenföl in Chloroform entsteht ein chlorhaltiges Produkt (Krystalle, F: 150–160°), das durch Wasser oder Alkohol in HCl und Phenyl-phenylimino-disulfazolidon („Phenylsenföloxyd").



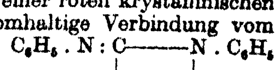
$$\begin{array}{l}C_6H_5 . N : C\text{———}N . C_6H_5\\ \qquad\qquad\ |\qquad\quad |\\ \qquad\qquad S . S . CO\end{array}$$

(Syst. No. 4445) zerlegt wird (Helmers, *B.* **20,** 786; vgl. Hantzsch, Wolvekamp, *A.* **331,** 279). Beim Versetzen einer Lösung von Phenylsenföl in dem 3-fachen Volumen Chloroform mit der gleichen Gewichtsmenge Brom in dem 3-fachen Volumen Chloroform erhielten Proskauer, Sell (*B.* **9,** 1262) eine tieforangerot gefärbte krystallinische Masse, die beim Kochen mit Alkohol oder Eisessig Phenyl-phenylimino-thion-disulfazolidin („Phenylsenfölsulfid")



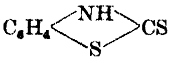
$$\begin{array}{l}C_6H_5 . N : C\text{———}N . C_6H_5\\ \qquad\qquad\ |\qquad\quad |\\ \qquad\qquad S . S . CS\end{array}$$

(Syst. No. 4445) neben anderen Produkten lieferte. Helmers (*B.* **20,** 788) erhiel bei der Einw. von Brom auf Phenylsenföl in Chloroform oder Essigsäure unter ähnlichen Bedingungen nach intermediärem Auftreten einer roten krystallinischen Verbindung eine in hellgelben Blättchen krystallisierende bromhaltige Verbindung vom Schmelzpunkt 190°, die beim Erwärmen mit Alkohol in Phenylphenylimino-disulfazolidon („Phenylsenföloxyd")

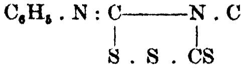


$$\begin{array}{l}C_6H_5 . N : C\text{———}N . C_6H_5\\ \qquad\qquad\ |\qquad\quad |\\ \qquad\qquad S . S . CO\end{array}$$

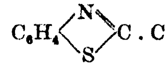
(Syst. No. 4445) überging. Die Einw. von Brom auf Phenylsenföl in Chloroformlösung in Gegenwart von wasserhaltigem Methylalkohol oder Athylalkohol führt zur Bildung von 2·4-Dibrom-carbanilsäuremethylester bezw. -äthylester (Syst. No. 1670) neben einer geringen Menge einer bei 192° schmelzenden, in tiefgelben Nadeln krystallisierenden, schwefelhaltigen Verbindung, die beim Kochen mit Alkohol in bromwasserstoffsaures Phenyl-phenylimino-disulfazolidon (Syst. No. 4445) übergeht (Fromm, Heyder, *B.* **42,** 3800 ; vgl. Freund, Bachrach, *A.* **285,** 196 ; Hantzsch, Wolvekamp, *A.* **331,** 279). Lässt man eine mit Chlorwasserstoff gesättigte Lösung von Phenylsenföl in absol. Athylalkohol oder Isobutylalkohol stehen, so scheidet sich allmählich salzsaures Anilin ab (Pinner, *B.* **14,** 1083). Phenylsenföl liefert beim Erhitzen mit Schwefel im geschlossenen Rohr auf 250–260° 2-Thion-benzthiazolin


$C_6H_4\!\left\langle\begin{matrix}NH\\S\end{matrix}\right\rangle\!CS$

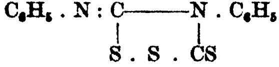
(Syst. No. 4278) (Jacobson Frankenbacher, *B.* **24,** 1405). Beim Leiten von Schwefeltrioxyddämpfen über Phenylsenföl entsteht die Verbindung $C_7H_5O_3NS_2$ (*S.* 458) (Magatti, *B.* **11,** 2267). Lässt man zu Phenylsenföl in der Wärme tropfenweise Chlorsulfonsäure fliessen, so bilden sich wenig Phenyl-phenylimino-thion-disulfazolidin


$$\begin{array}{l}C_6H_5\,.\,N:C\text{———}N\,.\,C_6H_5\\ \qquad\qquad\;\,|\qquad\qquad|\\ \qquad\qquad\;S\,.\,S\,.\,CS\end{array}$$

(Syst. No. 4445) und eine Verbindung $C_7H_7O_4NS_2$ (*S.* 459) (Pawlewski, *B.* **22,** 2200). Chlorschwefel wirkt bei erhöhter Temperatur auf Phenylsenföl unter Bildung geringer Mengen Phenylisocyanid-dichlorid (*S.* 447) ein (A. W. Hofmann, *B.* **13,** 9). Beim Erhitzen von Phenylsenföl mit PCl_5 im geschlossenen Rohr auf 160° entstehen Phenylisocyanid-dichlorid und 2-Chlorbenzthiazol

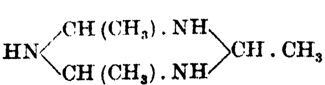
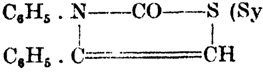

$C_6H_4\!\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle\!C\,.\,Cl$

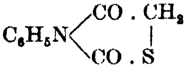
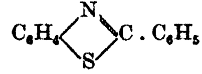
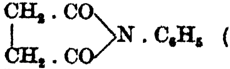
(Syst. No. 4195) (A. W. Hof., *B.* **12,** 1127 ; **13,** 8). Phenylsenföl liefert beim Erhitzen mit Wasser im geschlossenen Rohr auf 150° (Cain, Cohen, *Soc.* **59,** 328) oder beim Kochen mit Wasser in Gegenwart von Alkalien (Bamberger, *B.* **14,** 2642) CO_2, H_2S und Thiocarbanilid. Phenylsenföl verbindet sich direkt mit Ammoniak zu Phenylthioharnstoff (*S.* 388) (A. W. Hof., *J.* 1858, 349 ; *C.r.* **47,** 424), mit Hydroxylamin zu N′-Oxy-N-phenyl-thioharnstoff (*S.* 412) (E. Fischer, *B.* **22,** 1934 ; Tiemann, *B.* **22,** 1939 ; Voltmer, *B.* **24,** 378 ; V. D. Kall, *A.* **263,** 261). Aus äquimolekularen Mengen Phenylsenföl und Hydrazinhydrat in Alkohol unter Kühlung entsteht 4-Phenyl-thiosemicarbazid (*S.* 412) (Pulvermacher, *B.* **26,** 2812 ; **27,** 615 ; vgl. Busch, *B.* **42,** 4600). Beim Kochen von 2 Mol.-Gew. Phenylsenföl mit 1 Mol.-Gew. Hydrazinsulfat und Natriumcarbonat in wässrig-alkoholischer Lösung auf dem Wasserbade bildet sich Hydrazin-N . N′-bis-thiocarbonsäure-anilid (*S.* 414) (Freund, Wischewiansky, *B.* **26,** 2880). Beim Erhitzen von 1 Mol.-Gew. Phenylsenföl mit 1 Mol.-Gew. rotem Quecksilberoxyd auf 170° bildet sich Phenylisocyanat (*S.* 437) (Kühn, Liebert, *B.* **23,** 1536 ; vgl. A. W. Hof., *B.* **2,** 455). Beim Erwärmen von Phenylsenföl mit der gleichen Gewichtsmenge $AlCl_3$ auf dem Wasserbade tritt der Geruch nach Phenylisocyanid auf ; zerlegt man das hierbei erhaltene Reaktionsprodukt mit Wasser, so erhält man Phenyl-phenylimino-thion-disulfazolidin (" Phenylsenfölsulfid ")

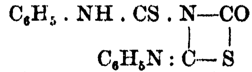

$$\begin{array}{l}C_6H_5\,.\,N:C\text{———}N\,.\,C_6H_5\\ \qquad\qquad\;\,|\qquad\qquad|\\ \qquad\qquad\;S\,.\,S\,.\,CS\end{array}$$

(Syst. No. 4445) (Friedmann, Gattermann, *B.* **25,** 3526 ; vgl. Ga., *J. pr.* [2] **59,** 575).

Beispiele für die Einwirkung organischer Verbindungen. Phenylsenföl addiert sich an aromatische Kohlenwasserstoffe oder Phenoläther bei Gegenwart von $AlCl_3$ zu Thiocarbonsäure-aniliden ; so z. *B.* entsteht mit Benzol Thiobenzanilid (*S.* 269), mit Anisol 4-Methoxy-thiobenzoesäure-anilid (*S.* 503) (Friedmann, Gattermann, *B.* **25,** 3525 ; Tust, Ga., *B.* **25,** 3528 ; Ga., *J. pr.* [2] **59,** 572). Halogensubstituierte aromatische Kohlenwasserstoffe reagieren mit Phenylsenföl in Gegenwart von $AlCl_3$ meistens nicht sehr glatt, dagegen verläuft die Reaktion mit halogensubstituierten Phenoläthern sehr leicht ; o-Chlor-anisol liefert z. *B.* bei gelindem Erwärmen auf dem Wasserbade 3-Chlor-4-methoxy-thiobenzoesäure-anilid (Ga., *J. pr.* [2], **59,** 583). Beim Erhitzen von Phenylsenföl mit gesättigten einwertigen aliphatischen Alkoholen entstehen Thiocarbanilsäureester (Orndorff, Richmond, *Am.* **22,** 458) ; z. B. mit Athylalkohol Thiocarbanilsäure-O-äthylester (*S.* 386) (A. W. Hofmann, *B.* **2,** 120 ; **3,** 772 ; Bamberger, *B.* **15,** 2164 ; Fromm, *B.* **42,** 1957). Thiocarbanilsäure-O-äthylester entsteht nach R. Schiff (*B.* **9,** 1316) auch aus Phenylsenföl beim Stehen mit alkoh. Kali bei gewöhnlicher Temperatur. Beim Kochen mit alkoh. Kali wird Phenylsenföl in Thiocarbanilid und dann in Carbanilid übergeführt (A. W. Hofmann, *Proc. Royal Soc. London,* **9,** 276). Bei der Einw. von Glycerin auf Phenylsenföl entsteht Thiocarbanilid (Tessmer, Volkmann, *B.* **18,** 972 ; vgl. Orndorff, Richmond, *Am.* **22,** 470). Phenylsenföl reagiert nicht mit Phenol, Hydrochinon, Pyrogallol und nicht mit aromatischen Alkoholen wie Benzylalkohol unter Bildung eines Thiocarbanilsäureesters ; mit Phenol wird als Reaktionsprodukt nur Thiocarbanilid erhalten (Orn., Rich., *Am.* **22,** 470, 471, 472 ; vgl. Rivier, *Bl.* [3] **35,** 841). Aus Phenylsenföl und Mercaptanen entstehen Dithiocarbanilsäureester, z. B. mit Äthylmercaptan Dithiocarbanilsäureäthylester (*S.* 416) (A. W. Hof., *B.* **2,** 120), mit Benzylmercaptan Dithiocarbanilsäurebenzylester (*S.* 416) (Fromm, Bloch, *B.* **32,** 2213).

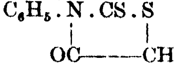
Phenylsenföl gibt mit Aldehydammoniak  $\mathrm{HN}\!\left\langle\begin{matrix}\mathrm{CH(CH_3).NH}\\\mathrm{CH(CH_3).NH}\end{matrix}\right\rangle\!\mathrm{CH.CH_3}$ (Syst. No. 3796) in siedender alkoholischer Lösung (Dixon, *Soc.* **53,** 416; vgl. R. Schiff, *B.* **9,** 567) oder beim Zusammenschmelzen (Dix, *Soc.* **61,** 518 Anm.) eine Verbindung $C_{11}H_{15}N_3S$ (Syst. No. 3796). Beim Erwärmen von Phenylsenföl mit Isovaleraldehydammoniak (Bd. I, *S.* 686) in Alkohol wird eine Verbindung $C_{17}H_{27}N_3S$ (*S.* 459) erhalten (Dixon, *Soc.* **53,** 417). Bei schwachem Erwärmen einer verdünnten alkoholischen Lösung von Phenylsenföl mit Benzalchloralammoniak (*Bd.* VII, *S.* 214) entstehen sofort Benzaldehyd, Chloral und Phenylthioharnstoff (R. Schiff, *B.* **11,** 2166). Phenylsenföl gibt bei der Einw. von α-Benzaldoxim (*Bd.* VII, *S.* 218) in Toluol Thiocarbanilid; dieses entsteht auch bei der Einw. von β-Benzaldoxim (*Bd.* VII, *S.* 221) auf Phenylsenföl (Pawlewski, *B.* **37,** 158). Reaktion von Phenylsenföl mit Campheroxim: Paw., *B.* **37,** 160. Beim Erhitzen von Phenylsenföl mit ω-Brom-acetophenon und Alkohol im geschlossenen Rohr auf 110° entsteht 2-Oxo-3, 4-diphenyl-thiazolin  $\begin{array}{l}\mathrm{C_6H_5.N}—\mathrm{CO}—\mathrm{S}\\ \qquad\ \ |\qquad\quad\ |\\ \mathrm{C_6H_5.C}=\!=\!=\mathrm{CH}\end{array}$ (Syst. No. 4279) (v. Walther, Griefenhagen, *J. pr.* [2] **75,** 204).

Beim Erhitzen von Phenylsenföl mit wasserfreier Essigsäure im geschlossenen Rohr auf 135–140° entstehen Acetanilid und COS, und bei Anwesenheit von Wasser ausserdem noch Carbanilid, H_2S und CO_2 (Werner, *Soc.* **59,** 544; vgl. Claus, Völtzkow, *B.* **14,** 445; Gumpert, *J. pr.* [2] **32,** 294; Cain, *Soc.* **59,** 327); analog verläuft die Reaktion mit Propionsäure mit Ameisensäure wird neben Formanilid und Carbanilid auch eine geringe Menge Thiocarbanilid erhalten (Wer.). Erhitzt man Phenylsenföl mit Chloressigsäure auf 125°, so bildet sich eine Verbindung C_8H_8ONCl vom Schmelzpunkt 134° (wahrscheinlich Chloracetanilid) (Völtzkow, *B.* **13,** 1580; Libermann, *A.* **207,** 141; Claus, V., *B.* **14,** 445); beim Erhitzen von Phenylsenföl mit Chloressigsäure auf 150° tritt Verharzung ein; erhitzt man Phenylsenföl mit Chloressigsäure in Gegenwart von Alkohol oder Äther, so bildet sich 3-Phenyl-2. 4-dioxo-thiazolidin ("Phenylsenfölglykolid")  $\mathrm{C_6H_5N}\!\left\langle\begin{matrix}\mathrm{CO.CH_2}\\|\\\mathrm{CO.S}\end{matrix}\right.$ (Syst. No. 4298) (Lieb, Vö., *B.* **13,** 278; Lieb, *A.* **207,** 140, 141). Beim Erwärmen von Phenylsenföl mit Dichloressigsäure entsteht Dichloracetanilid (*S.* 244) (Pawlewski, *B.* **32,** 1426). Phenylsenföl gibt beim Kochen mit Thioessigsäure Acetanilid (Paw., *B.* **32,** 1426; vgl. Wheeler, Merriam, *Am. Soc.* **23,** 298). Phenylsenföl reagiert mit salzsaurem Butyramidin (*Bd.* II, *S.* 276) in Kalilauge unter Bildung von N-Anilinothioformyl-butyramidin (*S.* 400) (Pinner, Die Imidoäther und ihre Derivate [Berlin, 1892], *S.* 125); analog verläuft die Reaktion mit Onanthamidin (*Bd.* II, *S.* 341) (Pinner, *B.* **28,** 476). Phenylsenföl liefert beim Erhitzen mit Benzoesäure Benzanilid (*S.* 262) (Krafft, Karstens, *B.* **25,** 458; Freundler, *Bl.* [3] **31,** 631). Durch Erhitzen von Phenylsenföl mit Benzoesäureanhydrid auf 230° wird Dibenzoylanilin (*S.* 274) erhalten (Kay, *B.* **26,** 2852). Beim Erhitzen von Phenylsenföl mit Benzoylchlorid auf 250° bis 300° entsteht in geringer Menge 2-Phenyl-benzthiazol  $\mathrm{C_6H_4}\!\left\langle\begin{matrix}\mathrm{N}\\\mathrm{S}\end{matrix}\right\rangle\!\mathrm{C.C_6H_5}$ (Syst. No. 4199) (A. W. Hof., *B.* **13,** 17). Phenylsenföl vereinigt sich mit Benziminomethyläther (*Bd.* IX, *S.* 270) zu N-Anilinothioformyl-benziminomethyläther (*S.* 401), analoge Verbindungen entstehen mit Benziminoäthyläther und Benziminoisobutyläther (Wheeler, Sanders, *Am. Soc.* **22,** 371, 372, 373). Phenylsenföl gibt mit salzsaurem Benzamidin (*Bd.* IX, *S.* 280) und Natronlauge N-Anilinothioformylbenzamidin (*S.* 401) (Pinner, *B.* **22,** 1609), analog verläuft die Reaktion mit 3-Nitrobenzamidin (Pinner, *B.* **28,** 484). Phenylsenföl reagiert mit Benzamidoxim unter Bildung von Benzoesaure-[ω-phenyl-thioureid]-oxim (*S.* 401) (Krüger, *B.* **18,** 1060), analog verläuft die Reaktion auch mit p-Tolamidoxim (Schubart, *B.* **22,** 2435) und asymm. m-Xylysäureamidoxim (Oppenheimer, *B.* **22,** 2448). Beim Vermischen der alkoh. Lösungen von Phenylsenföl und Benzhydrazid bildet sich 4-Phenyl-1-benzoyl-thiosemicarbazid (*S.* 414) (Marckwald, Bott, *B.* **29,** 2916). Phenylsenföl gibt mit Thiobenzoesäure auf dem Wasserbade CS_2 und Benzanilid (Wheeler, Merriam, *Am. Soc.* **23,** 298). Beim Erhitzen von Phenylsenföl mit Malonsäure bilden sich Carbanilid, Acetanilid und COS (Bénech, *C.r.* **130,** 922). Beim Hinzufügen von Phenylsenföl zur alkoh. Lösung von Natriummalonsäure-diäthylester wird Methan-dicarbonsäurediäthylester-thiocarbonsäureanilid (*S.* 316) erhalten (Michael, *J. pr.* [2] **35,** 450, 451). Gibt mit Natriumcyanessigester in Alkohol Cyanmalonsäureäthylester-thioanilid (*S.* 316) (Ruhemann, *Soc.* **93,** 626). Beim Erhitzen von Phenylsenföl mit Bernsteinsäure entsteht N-Phenylsuccinimid  $\begin{matrix}\mathrm{CH_2.CO}\\|\\\mathrm{CH_2.CO}\end{matrix}\!\Big\rangle\mathrm{N.C_6H_5}$ (Syst. No. 3201), mit Sebacinsäure Sebacinsäuredianilid (*S.* 304) (Bén., *C.r.*, **130,** 922, 923). Phenylsenföl gibt mit der Natriumverbindung des Carbamidsäure-äthylesters in absol. Äther N-Phenyl-N′-carbäthoxy-thioharnstoff (*S.* 402) uud die Natriumverbindung der Anhydrodiphenyldithiobiuretcarbonsäure



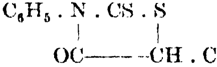
$$\begin{array}{rcl} C_6H_5.NH.CS.N & \text{—} & CO \\ | & & | \\ C_6H_5N:C & \text{—} & S \end{array}$$

(Syst. No. 4298) (Ruhemann, Priestley, *Soc.* **95,** 455). Beim Kochen von Phenylsenföl mit dem Silbersalz des Cyanamids in absol. Alkohol entsteht O-Äthyl-N-phenyl-N′-cyan-isoharnstoff (?) (*S.* 368) (Kämpf, *B.* **37,** 1682, 1684). Phenylsenföl gibt mit Natriumcyanamid, verteilt in Alkohol, und Isobutyljodid S-Isobutyl-N-phenyl-N′-cyanisothioharnstoff (*S.* 409) (Hecht, *B.* **25,** 822). Beim Erwärmen von 3 Tln. Phenylsenföl mit 2 Tln. Guanidincarbonat auf 100° unter Zusatz von absol. Alkohol entsteht N-Phenyl-N′-guanyl-thioharnstoff (*S.* 403), neben Thiocarbanilsäure-O-äthylester (*S.* 386) (Bamberger, *B.* **13,** 1581 ; **14,** 2638 ; **15,** 2165 ; vgl. auch Cramer, *B.* **34,** 2602 ; Michael, *J. pr.* [2] **49,** 42). Phenylsenföl gibt mit S-Methyl-isothioharnstoff (*Bd.* III, *S.* 192) S^1-Methyl-N^c-phenylisodithiobiuret (*S.* 405) (Johnson, Bristol, *Am.* **30,** 172). Phenylsenföl kondensiert sich mit Thioglykolsäure (*Bd.* III, *S.* 244) zu Phenyl-rhodaninsäure



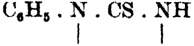
$$\begin{array}{lcr} C_6H_5.N & .CS. & S \\ | & & | \\ OC & \text{———} & CH_2 \end{array}$$

(Syst. No. 4298) (Andreasch, Zipser, *M.* **24,** 500), mit Thiomilchsäure (*Bd.* III, *S.* 289) zu Methylphenyl-rhodaninsäure



$$\begin{array}{lcl} C_6H_5.N & .CS. & S \\ | & & | \\ OC & \text{———} & CH.CH_3 \end{array}$$

(Syst. No. 4298) (And., Zi., *M.* **25,** 178). Phenylsenföl reagiert bei längerem Stehen mit β-Amino-crotonsäureäthylester (*Bd.* III, *S.* 654) unter Bildung von β-Imino-äthylmalonsäure-äthylester-thioanilid (*S.* 535) ; bei erhöhter Temperatur entsteht daneben Methyl-phenyl-thiouracil



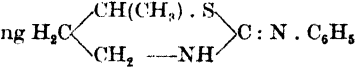
$$\begin{array}{l} C_6H_5.N.CS.NH \\ \quad | \qquad\quad | \\ OC.CH:C.CH_3 \end{array}$$

(Syst. No. 3588) (Behrend, Hesse, *A.* **329,** 342 ; vgl. Beh., Meyer, Buchholz, *A.* **314,** 224). Beim Erhitzen von Phenylsenföl mit Diacetonitril (*Bd.* III, *S.* 660) auf 140–150° wird β-[Anilinothioformylimino]-buttersäure-nitril

$$C_6H_5.NH.CS.N:C(CH_3)CH_2.CN$$

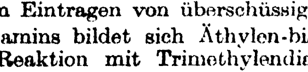
(*S.* 406) erhalten ; analog verläuft die Reaktion mit Benzoacetodinitril (*Bd.* X, *S.* 681) (Hübner, *J. pr.* [2] **79,** 68).

Mit aliphatischen Mono- und Dialkylaminen vereinigt sich Phenylsenföl zu den entsprechenden Thioharnstoffen ; z. B. mit Äthylamin zu N-Äthyl-N′-phenyl-thioharnstoff (*S.* 390) (Weith, *B.* **8,** 1524), mit Dimethylamin zu N . N-Dimethyl-N′-phenyl-thioharnstoff (*S.* 390) (Dixon, *Soc.* **61,** 538 ; Billeter, *B.* **26,** 1685). Beim Schütteln der unter Kühlung mit Phenylsenföl versetzten benzolischen Lösung von γ-Chlor-butylamin (*Bd.* IV, *S.* 159) entsteht die Verbindung



$$H_2C\left<\begin{array}{l} CH(CH_3).S \\ CH_2\text{——}NH \end{array}\right>C:N.C_6H_5$$

(Syst. No. 4271) (Luchmann, *B.* **29,** 1430). Mit Anilin verbindet sich Phenylsenföl bei gelindem Erwärmen zu Thiocarbanilid (A. W. Hofmann, *J.* 1858, 349 ; *C.r.* **47,** 424). Beim Zusammengiessen molekularer Mengen Phenylsenföl und Methylanilin, auch in stark verdünnter alkoholischer Lösung, entsteht N-Methyl-N . N′-diphenyl-thioharnstoff (*S.* 420) ; erhitzt man Phenylsenföl mit Methylanilin im geschlossenen Rohr auf ca. 250°, so erhält man Thiocarbanilid und Dimethylanilin (Gebhardt, *B.* **17,** 2089, 2090). Mit Diphenylamin reagiert Phenylsenföl erst nach mehrtägigem Erhitzen auf ca. 280° unter Bildung einer geringen Menge Triphenylthioharnstoff (*S.* 432) (Geb., *B.* **17,** 2092 ; vgl. auch *B.* **17,** 3035). Phenylsenföl gibt mit N . N′-Diphenylguanidin (*S.* 369) in etwas Benzol in der Kälte N-Phenyl-N′-(diphenyl-guanyl)-thioharnstoff (*S.* 405) (Rathke, *B.* **12,** 774). Aus N″-Amino-N . N′-diphenyl-guanidin (*S.* 384) und Phenylsenföl in wenig Alkohol bildet sich 4-Phenyl-1-(diphenyl-guanyl)-thiosemicarbazid (*S.* 414) (Busch, Bauer, *B.* **33,** 1066). 2-Methyl-4-phenyl-thiosemicarbazid (*S.* 412) liefert beim Erhitzen mit Phenylsenföl auf etwa 100° 3-Methyl-2·5-bis-phenylimino-1 . 3 . 4-thiodiazoltetrahydrid[1]



$$\begin{array}{rcl} CH_3.N & \text{———} & NH \\ | & & | \\ C_6H_5.N:C & \text{—S—} & C:N.C_6H_5 \end{array}$$

(Syst. No. 4560) (Marckwald, Sedlaczek, *B.* **29,** 2921). Beim Eintragen von überschüssigem Phenylsenföl in die kalte alkoh. Lösung des Äthylendiamins bildet sich Äthylen-bis-(ω-phenyl-thioharnstoff) (*S.* 406), analog verläuft die Reaktion mit Trimethylendiamin (Lellmann, Würthner, *A.* **228,** 234, 236). Phenylsenföl reagiert in alkoh. Losung mit der äquimolekularen Menge *o*-Phenylendiamin unter Bildung von N-Phenyl-N′-(2-amino-phenyl)-thioharnstoff (Syst. No. 1752) ; 2 Mol.-Gew. Phenylsenföl geben mit 1 Mol.-Gew. *o*-Phenylendiamin in alkoh. Lösung *o*-Phenylen-bis-(ω-phenyl-thioharnstoff) (Syst. No. 1752) ; analog verlaufen die Reaktionen mit *m*- und *p*-Phenylendiamin (Lellmann, *A.* **221,** 28 ; Lell. Würthner, *A.* **228,** 199). Phenylsenföl reagiert mit β-Oxy-äthylamin (*Bd.* IV, *S.* 274) unter Bildung von N-(β-Oxy-äthyl)-N′-phenyl-thioharnstoff (*S.* 398) (Knorr, Rössler, *B.* **36,** 1280). Bei der Reaktion zwischen Phenylsenföl und Glykamin (*Bd.* IV, *S.* 305) in

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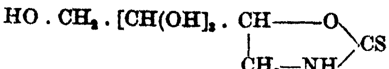
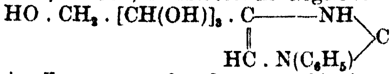
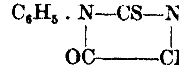
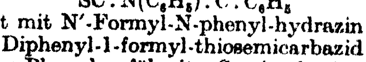
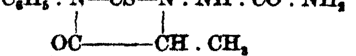
[1] So formuliert auf Grund einer Privatmitteilung von Busch ; vgl. auch B., Holzmann, *B.* **34,** 344 ; *B.*, Limpach, *B.* **44,** 1573.

 $\begin{array}{l} \mathrm{HO.CH_2.[CH(OH)]_3.CH{-}O} \\ \qquad\qquad\qquad\qquad\qquad\quad \mathrm{>CS} \\ \qquad\qquad\qquad\quad \mathrm{CH_2{-}NH} \end{array}$ siedender Pyrindinlösung entsteht die Verbindung (Syst. No. 4300) und Thiocarbanilid (Roux, *A. ch.* [8] **1**, 113; vgl. Maquenne, Roux, *C. r.* **134**, 1591). Phenylsenföl liefert mit Aminoacetal (*Bd.* IV, *S.* 308) N-Phenyl-N′-acetalyl-thioharnstoff (*S.* 399) (Wohl, Marckwald, *B.* **22**, 569). Aus Phenylsenföl und Diacetonamin (*Bd.* IV, *S.* 322) entsteht Methyl-[β-(ω-phenyl-thioureido)-isobutyl]-keton (*S.* **399**) (W. Traube, *B.* **27**, 279); analog verläuft die Reaktion mit Methyl-(ε-amino-*n*-amyl)-keton (*Bd.* IV, *S.* 324) (Gabriel, *B.* **42**, 1257) und Methyl-(ζ-amino-n-hexyl)-keton (*Bd.* IV, *S.* **325**) (Gabr., *B.* **42**, 4055). Die Einw. von Phenylsenföl auf salzsaures Glykosamin (*Bd.* IV, *S.* 328) in Aceton in Gegenwart von Natriumcarbonat führt zu der Verbindung  $\begin{array}{l} \mathrm{HO.CH_2.[CH(OH)]_3.C{=}{=}{=}NH} \\ \qquad\qquad\qquad\qquad\qquad\qquad \mathrm{>CS} \\ \qquad\qquad\qquad\qquad \mathrm{HC.N(C_6H_5)} \end{array}$ (Syst. No. 3638) (Neuberg, Wolff, *B.* **34**, 3843). Beim Zusammenschmelzen von Glycin mit Phenylsenföl entsteht 3-Phenyl-2-thiohydantoin  $\begin{array}{l} \mathrm{C_6H_5.N{-}CS{-}NH} \\ \qquad\quad | \qquad\qquad | \\ \qquad \mathrm{OC{-}{-}{-}CH_2} \end{array}$ (Syst. No. 3587) (Aschan, *B.* **17**, 424); analog bildet N-Phenylglycin (*S.* **468**) beim Erhitzen mit Phenylsenföl auf 80° 1·3-Diphenyl-2-thiohydantoin (Syst. No. 3587) (Aschan, Zilliacus, *Öf. Fi.* **29**, 165). Phenylsenföl verbindet sich mit Glycinäthylester in Äther zu Anilinothioformyl-glycin-äthylester (*S.* 405) (E. Fischer, *B.* **34**, 439). Aus Phenylsenföl und Äthylaminoacetonitril (*Bd.* IV, *S.* 349) in Chloroformlösung entsteht N-Äthyl-N-anilinothioformyl-glycin-nitril (*S.* 406) (Knoevenagel, Mercklin, *B.* **37**, 4092). Fügt man zu Alanin, gelöst in der äquivalenten Menge konz. Kalilauge, die äquimolekulare Menge Phenylsenföl in alkoh. Lösung, so erhält man α-[ω-phenyl-thioureido]-propionsaures Kalium (*S.* 406) (Marckwald, Neumark, Stelzner, *B.* **24**, 3280); beim Zusammenschmelzen von Alanin und Phenylsenföl wird 5-Methyl-3-phenyl-2-thiohydantoin (Syst. No. 3587) erhalten (Aschan, *B.* **16**, 1544; **17**, 421); Phenylsenföl verbindet sich mit *d*-Glykosaminsäure (*Bd.* IV, *S.* 522) in Acetonlösung bei Gegenwart von Alkali zu N-Anilinothioformyl-*d*-glykosaminsäure (*S.* 406) (Neuberg, Wolff, Neimann, *B.* **35**, 4013). Phenylsenföl gibt mit Anthranilsäure in alkoholischer, schwach alkalischer Lösung 2-[ω-Phenyl-thioureido]-benzoesäure (Syst. No. 1897) (McCoy, *Am.* **21**, 146, 147), beim Erhitzen mit *m*-Amino-benzoesäure im geschlossenen Rohr auf 100° 3-[ω-Phenyl-thioureido]-benzoesäure vom Zersetzungspunkt 260–262° (Syst. No. 1905) (Aschan, *B.* **17**, 428).

Phenylsenföl verbindet sich bei gewöhnlicher Temperatur mit Methylhydrazin zu 2-Methyl-4-phenyl-thiosemicarbazid (*S.* 412) (v. Brüning, *A.* **253**, 11; Busch, Opfermann, Walther, *B.* **37**, 2321); analog verläuft die Reaktion mit Hydrazinoessigsäure (*Bd.* IV, *S.* 556) (Traube, Hoffa, *B.* **31**, 168). Mit N.N′-Dimethyl-hydrazin (*Bd.* IV, *S.* 547) entsteht 1·2-Dimethyl-4-phenyl-thiosemicarbazid (*S.* 413) (Knorr, Köhler, *B.* **39**, 3264). Phenylsenföl liefert mit Phenylhydrazin in Alkohol bei niedriger Temperatur 2·4-Diphenyl-thiosemicarbazid (Syst. No. 2037) (Marckwald, *B.* **25**, 3106; Busch, Holzmann, *B.* **34**, 320); ohne Kühlung entsteht vorwiegend 1, 4-Diphenyl-thiosemicarbazid (Syst. No. 2040) (E. Fischer, *A.* **190**, 122; Busch, *B.* **42**, 4600). Mit Phenylhydrazin in ameisensaurer oder essigsaurer alkoholischer Lösung entsteht dagegen selbst bei höherer Temperatur (50°) vorweigend 2·4-Diphenyl-thiosemicarbazid; in absol. Äther oder Benzol selbst bei 0° überwiegend 1·4-Diphenyl-thiosemicarbazid (Busch, *B.* **42**, 4599). Mit Benzalhydrazin in siedendem Alkohol wird 4-Phenyl-1-benzal-thiosemicarbazid (*S.* 413) erhalten; analog verläuft die Reaktion mit Salicylalhydrazin (*Bd.* VIII, *S.* 50) (Curtius, Franzen, *B.* **35**, 3236, 3237). Bei 20-24-stdg. Erhitzen äquimolekularer Mengen Phenylsenföl und Acetonphenylhydrazon (Syst. No. 1954) im Wasserbade entsteht 1-Isopropyliden-2·4-diphenyl-thiosemicarbazid (Syst. No. 2038) (Vahle, *B.* **27**, 1514). Bei 12-14-stdg. Erhitzen von äquimolekularen Mengen Phenylsenföl und α-Benzal-phenylhydrazin (Syst. No. 1958) im geschlossenen Rohr auf 175–180° wird die Verbindung  $\begin{array}{l} \mathrm{C_6H_5.N{-}{-}{-}{-}N} \\ \qquad\qquad | \qquad\qquad \| \\ \qquad\qquad \mathrm{SC.N(C_6H_5).C.C_6H_5} \end{array}$ [1] (Syst. No. 3876) gebildet (Vahle, *B.* **27**, 1514). Phenylsenföl gibt mit N′-Formyl-N-phenyl-hydrazin (Syst. No. 2009) im geschlossenen Rohr bei 180° 2·4-Diphenyl-1-formyl-thiosemicarbazid (Syst. No. 2038) (Vahle, *B.* **27**, 1517). Beim Erhitzen von Phenylsenföl mit α-Semicarbazino propionsäure-äthylester (*Bd.* IV, *S.* 557) in Essigester entsteht 1-Ureido-5-methyl-3-phenyl-2-thio-hydantoin  $\begin{array}{l} \mathrm{C_6H_5.N{-}CS{-}N.NH.CO.NH_2} \\ \qquad\quad | \qquad\qquad | \\ \qquad \mathrm{OC{-}{-}{-}CH.CH_3} \end{array}$ (Syst. No. 3587) (Bailey, *Am. Soc.* **26**, 1012). Kocht man α-Hydrazino-isobuttersäure mit 1 Mol.-Gew. Phenylsenföl in wässrig-alkoholischer Lösung etwa 20 Minuten, so erhält man 1-Amino-5·5-dimethyl-3-phenyl-2-thio-hydantoin (Syst. No.

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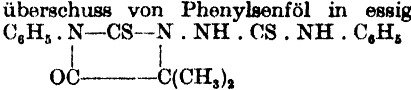
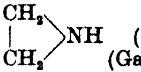
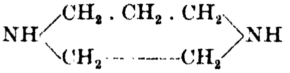
[1] Zur Formulierung vgl. die nach dem Literatur-Schlusstermin der 4. Aufl. dieses Handbuches [1.1.1910] erschienene Arbeit von Busch, Schneider (*J. pr.* [2] **89**, 314).

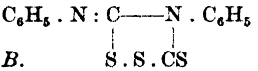
3587) (Bail., *Am. Soc.* **26,** 1020). Kocht man α-Hydrazino-isobuttersäure mit einem überschuss von Phenylsenföl in essigsaurer Lösung, so erhält man die Verbindung  (Bail., *Am. Soc.* **26,** 1015). Beim Zusammenbringen molekularer Mengen Phenylsenföl und N-Phenyl-hydrazin-N-essigsäure-äthylester (Syst. No. 2044) entsteht 1-[Carbäthoxy-methyl]-1·4-diphenyl-thiosemicarbazid (Syst. No. 2044) (Harries, *B.* **28,** 1227).

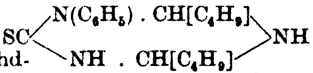
Phenylsenföl lässt sich durch Einw. von Methylmagnesiumjodid in äther. Lösung und nachfolgende Behandlung des Reaktionsproduktes mit Wasser und verd. Schwefelsäure in Thioacetanilid (*S.* 245) überführen; in analoger Weise werden mit anderen Alkyl- und Aryl-magnesiumverbindungen die entsprechenden Thioacylanilide erhalten (Sachs, Loevy, *B.* **36,** 586; *B.* **37,** 875).

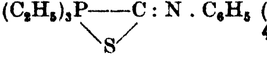
Phenylsenföl verbindet sich mit Äthylenimin  (Syst. No. 3035) zu Äthylen-imin-N-thiocarbonsäure-anilid (Syst. No. 3035) (Gabriel, Stelzner, *B.* **28,** 2935), analog verläuft die Reaktion mit Trimethylenimin (Syst. No. 3036) (Howard, Marckwald, *B.* **32,** 2035), Pyrrolidin (Syst. No. 3037) (Schlinck, *B.* **32,** 955), Piperidin (Syst. No. 3038)  (Gebhardt, *B.* **17,** 3039). Mit Äthylen-trimethylen-diamin (Syst. No. 3460) in Alkohol gibt Phenylsenföl Äthylen-trimethylen-diamin-N. N′-*bis*-[thiocarbonsäureanilid] (Syst. No. 3460) (Esch, Marckwald, *B.* **33,** 761). Durch Vermischen von Lösungen von Phenylsenföl und 2-Methyl-glyoxalin-dihydrid-(4·5) (Syst. No. 3461) in absol. Alkohol erhält man 2-Methyl-1-anilinothioformyl-glyoxalin-dihydrid-(4·5). (Syst. No. 3461) (Dixon, *Soc.* **69,** 34).

Umwandlungsprodukte ungewisser Konstitution aus Phenylsenföl.

Verbindung $C_7H_5O_3NS_2$. *B.* Aus Phenylsenföl und SO_3 (Magatti, *B.* **11,** 2267).—Krystalle (aus Benzol). F: 180–183° (Zers.). Unlöslich in Wasser, Alkohol, Äther, Eisessig, leicht löslich in siedendem Benzol, $CHCl_3$, Nitrobenzol. Unlöslich in Säuren und Alkalien.—Wird durch Alkalien leicht entschwefelt. Zerfällt beim Erhitzen mit Wasser im geschlossenen Rohr bei 100° in H_2S, CO_2 und Sulfanilsäure.

Verbindung $C_7H_7O_4NS_2$. *B.* Neben " Phenylsenfölsulfid "  (Syst. No. 4445) aus Phenylsenföl und Chlorsulfonsäure (Pawlewski, *B.* **22,** 2200).—Tafeln (aus Wasser). Schwer löslich in kochendem Wasser, fast unlöslich in starkem Alkohol.—Geht bei 130° oder im Exsiccator in eine Verbindung $C_7H_5O_3NS_2$ über.

Verbindung $C_{17}H_{27}N_3S$ =  (?). *B.* Beim Erwärmen von Phenylsenföl und Isovaleraldeyhd-ammoniak (*Bd.* I, *S.* 686) in Alkohol (Dixon, *Soc.* **53,** 417). — Nadeln (aus Alkohol). F: 152–153° (Zers.).'

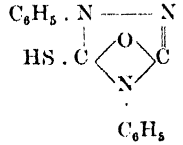
Phenylsenföl reagiert mit Triäthylphosphin (*Bd.* IV, *S.* 582) in Gegenwart von viel Äther unter Bildung der Verbindung  (*S.* 463) (A. W. Hofmann, *A. Spl.* **1,** 36; Hantzsch, Hibbert, *B.* **40,** 1511).

Beilstein, Vol. 12, Supplement, pages 261–262.

'*Thiokohlensäure-anil, Thiocarbanil, Phenylisothiocyanate, Phenylsenföl* $C_7H_5NS = C_6H_5 . N : CS$ (*S.* 453). *B.* Bildet sich leicht aus den Salzen der Dithiocarbanilsäure, so beim Erwärmen des sauren Kaliumsalzes mit Wasser (Rathke, *B.* **11,** 960), beim Erwärmen des Bleisalzes (M. Mayer, Fehlmann, *C.* 1910, II, 930; vgl. Heller, Bauer, *J. pr.* [2] **65,** 369), bei der Einw. von Chlorameisensäureester auf das Ammoniumsalz (Wheeler, Dustin, *Am.* **24,** 432; Andreasch, *M.* **27,** 1219). Durch Erhitzen von S-Trichlormethyl-N-phenyl-thiohydroxylamin $C_6H_5 . NH . S . CCl_3$ auf 125–130° (Johnson, Hemingway, *Am. Soc.* **38,** 1865). Aus dem Phenylimid des Triphenylphosphins $(C_6H_5)_3P : N . C_6H_5$ (Syst. No. 2272) in siedendem Schwefelkohlenstoff (Staudinger, J. Meyer, *Helv.* **2,** 644).

— *Darst.* Man fügt unter beständigem Rühren allmählich 56 g. Anilin zu einer gekühlten Mischung aus 54 g. Schwefelkohlenstoff und 90 cm^3 Ammoniak (D: 0·9) und behandelt die wässr. Lösung des entstandenen Ammoniumsalzes der Dithiocarbanilsäure mit Bleinitrat-Lösung (*Organic Syntheses, Coll.* Vol. I (New York, 1932), *S.* 437).—D_4^{25}: 1·1288; D_4^{35}: 1·1202; D_4^{50}: 1·1061 (Kurnakow, Shemtschushny, *Ph. Ch.* **83,** 494; *J. der Russ. Physik.-chem. Gesellschaft,* **44,** 1977). Viscosität bei 25°: 0·01397; bei 35°: 0·01199; bei 50°; 0·00978 g./cmsec. (Ku., Sh.). Oberflächenspannung zwischen 13·2° (41·5 dyn/cm.) und 152·2° (26·3 dyn/cm.): Bolle, Guye, *J. Chim. Phys.* **3** [1905], 41; vgl. a. Morgan, Chazal, *Am. Soc.* **35,** 1823. Kryoskopisches Verhalten in Schwefel: Beckmann, Platzmann, *Z. anorg. Ch.* **102,** 206. Dichte und Viscosität der Gemische mit Diäthylamin: Ku, Sh.

Phenylsenföl wird beim Leiten über eine auf 700° erhitzte Silberspirale nicht zersetzt (Staudinger, Endle, *B.* **46,** 1442). Liefert beim Erhitzen mit Eisenpulver in Maschinenöl auf 290° Benzonitril (Bayer & Co., D.R.P., 259,364 ; *C.* 1913, I, 1741 ; *Frdl.* **11,** 204) Beim Erhitzen mit Stickstoffwasserstoffsäure in Äther unter Druck auf 40–50° entsteht Thiocarbanilsäureazid, beim Erhitzen auf 60–70° erhält man 5-Amino-1-phenyl-tetrazol, (Syst. No. 4110) (Olivori-Mandala, Noto, *G.* **43,** I, 312 ; O.-M., *G.* **44,** I, 671 ; vgl. O.-M. *G.* **52,** I, 103 ; Stollé, *B.* **55,** 1291). Thiocarbanilsäure-O-Äthylester entsteht . . . bei gewöhnlicher Temperatur ; in guter Ausbeute bilden sich Thiocarbanilsäure-O-ester bei der Umsetzung von Phenylsenföl mit Natriumalkoholaten (Roshdestwenski, *J. der Russ. Physik.-chem. Gesell.* **41,** 1441 ; *C.* 1910, I, 910). Bei tagelangem Erwärmen von Phenylsenföl mit Phenol auf 80° entsteht Thiocarbanilsäure-O-phenylester (Schneider, Wrede, *B.* **47,** 2040). Phenylsenföl liefert mit Bleiphenolat in Phenol bei 100–110° Kohlensäurediphenylester-anil (Chem. Fabr. Ladenburg, D.R.P. 230,827 ; *C.* 1911, I, 601 ; *Frdl.*, **10,** 1322). Gibt mit Chloressigsäureanhydrid bei 160–180° 2·4-Dioxo-3-phenyl-thiazolidin und Chloracetanilid (Dubsky, Gränacher, *B.* **50,** 1689). Beim Erhitzen mit Harnstoff oder Thioharnstoff für sich oder in alkoh. Lösung entstehen N . N′-Diphenyl-thioharnstoff und Cyanamid (Pieroni, *G.* **42,** II, 184). Bei Einw. von 0·67 Mol. Benzilsäure in der Wärme entsteht 4-Phenylimino-3, 5, 5-triphenyl-thiazolidon-(2) (Syst. No. 4298), mit 1 Mol Benzilsäuremethylester und Natrium in Xylol Thiocarbanilsäure-O-methylester (*S.* 242) (Bettschart, Bistryzycki, *Helv.* **2,** 130). Liefert mit Benzilsäure in Eisessig-Schwefelsäure in der Kälte Thiocarbanilsäure-S-[α-carboxy-benzhydrylester] (*S.* 244) (Becker, Bi, *B.* **47,** 3151). Mit Natriumacetessigester in Äther entsteht die Natrium-verbindung des Acetylmalonsäureäthylester thioanilids (*S.* 280) (Worrall, *Am. Soc.* **40,** 418). Bei Einw. von Natriumbenzylacetessigester in siedendem Toluol und Behandlung des Reaktionsproduktes mit verd. Salzsäure erhält man eine Verbindung $(C_{15}H_{15}NS)_x$ (s.u.) (Wo., *Am. Soc.* **40,** 423). Liefert mit Iminodiessigsäure in siedendem Alkohol 3-Phenyl-2-thiohydantoinessigsäure-(1) (Bailey, Snyder, *Am. Soc.*, **37,** 941). Gibt mit ω-Phenyl-carbazinsäureäthylester (Syst. No. 2040) in alkoh. Kalilauge 1·4-Diphenyl-thiosemicarbazid-carbonsäure-(1)-äthylester,



5-Mercapto-1, 4-diphenyl-3·5-oxido-1 . 2 . 4-triazolin (s. nebenstehende Formel ; Syst. No. 3888) und Thiocarbanilsäure-O-äthylester (Busch, Limpach, *B.* **44,** 1575, 1580). Beim Erwärmen mit dem Phenylimid des Triphenylphosphins $(C_6H_5)_3P:N.C_6H_5$ bildet sich Triphenylphosphinsulfid $(C_6H_5)_3PS$ (Staudinger, J. Meyer, *Helv.* **2,** 644).

“ Polymers Benzylthioacetanilid ” $(C_{15}H_{15}NS)_x = (C_6H_5.CH_2.CH_2.CS.NH.C_6H_5)_x$ (?). *B.* Bei der Einw. von Natrium-benzylacetessigester auf Phenylsenföl in siedendem Toluol und nachfolgenden Behandlung des Reaktionsprodukte mit verd. Salzsäure (Worrall, *Am. Soc.*, **40,** 423).—Gelbe Krystalle. F. 222–223° (Zers.). Fast unlöslich in Alkohol und Benzol, ferner in Natronlauge und Salzsäure.’

This is an exhaustive and complete account of the subject up to 1919 ; further search must be made in the abstract indexes from 1919 onward. In order to complete this example, a search has been made in the American Chemical Abstracts, details of which are given below. The substance is not indexed under the name ‘ Phenyl mustard oil ’, although a cross reference is given to the approved name which is ‘ Isothiocyanic acid, phenyl ester ’.

In the entries on page 23 only those are given which are directly indexed under the particular compound sought ; much additional information may often be obtained from the entries generally under ‘ Isothiocyanic acid ’, particularly under the sub-heads ‘ aryl esters ’, ‘ esters ’ ; in the case of the 1927–1936 Collective Index there is an entry :—

“ ISOTHIOCYANIC ACID, ESTERS

“ Thesis : Die Darstellung aromatischer Senföle und Isocyanate und ihre Kondensation mit Guanidin, *28,* 1716^2.”

which might be of considerable interest.

In order to reduce this mass of information to a form convenient for reference, it is desirable to enter on a card each individual reference either from

Entries in the 1917–1926 Collective Index

Isothiocyanic Acid, Phenyl ester
addn. compds. with pyridine derivs., **18**: $3382^{2, 3, 4}$
compds. with alkylmethylenedihydro-pyridines and -quinolines, **18**: 2519^{9}
prepn. from thiocarbanilide, **20**: 1081^{5}, 1223^{3}
prepn. of, **20**: 3288^{2}

Entries in the 1927–1936 Collective Index

Isothiocyanic Acid, Phenyl ester
compd. with ICl_3, **26**: P. 1068^{6}
compressibility and ultrasonic velocity for, **30**: 7942^{2}
elec. moment of, **25**: 2611^{9}
elec. moment of, and deriv., **26**: 3969^{3}
parachor of, **24**: 1624^{7}
prepn. of, **21**: 67^{6}
Raman effect of, **24**: 4707^{3}, 5231^{8}
reaction with alphylhydrazines, **25**: 4862^{5}
reaction with aminoglucose, **24**: 5285^{3}
reaction with AsH_3, and with Ph_3, attempted, **24**: 5028^{5}
reaction with carbethoxyguanidine, **28**: 1665^{5}
reaction with cotarnine, **29**: 2961^{9}
reaction with guanidine, **23**: 3903^{4}
reaction with isatic acid, **21**: 587^{2}
reaction with PhLi and with PhNa, **27**: 1872^{2}
reaction with phenols, **24**: 80^{6}
reaction with phenols in presence of $AlCl_3$, **26**: 3239^{9}
reaction with PhMgBr, **23**: 3909^{1}
reaction with Na derivs. of esters of malonic and cyanoacetic acids, **27**: 5065^{5}
as reagent for identification of primary aromatic amines, **23**: 3445^{5}
refraction equivalent of, N valency and, **22**: 3346^{5}
system: diethylaniline-, surface tension and its temp. coeff., **29**: 6119^{2}
systems: methylaniline-, and diethylaniline-, **26**: 3159^{3}

Entries in the 1937-1946 Collective Index

Isothiocyanic acid, Phenyl ester, **37**: 4708^{5}
behaviour in anhyd. HF, **31**: 5705^{6}
compd. with 4-amino-1-diethyl-amino-2-butanol, **40**: 5699^{8}
formation from salts of $PhNHCS_2H$, **31**: 1377^{1}
mixts. with methylaniline or piperidine, f.-p. lowering of C_6H_6 by, **35**: 6175^{4}
oxidation of a mixt. of, and phenyl-guanidine, **33**: 5818^{4}
prepn. of, **34**: 6131^{5}
reaction with benzoin oxime, **35**: 6246^{5}
reaction with 4-(hydroxymethyl) antipyrine, **37**: 5404^{1}
reaction with methine enolbetaines, **31**: 3920^{2}
reaction with pyrazolone derivs. **31**: 1803^{8}
reactions with S and CS_2, **34**: 6487^{4}
spectrum of, **34**: 5755^{5}
system: $PhNH_2$ -- S --, **37**: 6532^{7}

Beilstein or from the Abstracts, with the whole of the data available from these sources. A reproduction of the card used in the author's laboratories is shown on page 24.

Having once made a complete search of this nature, the cards are filed together, and from the nature of the Beilstein and Abstract entries the worker can judge which are of sufficient value to warrant the study of the original papers to which they refer. The example taken was purposely selected for its simplicity; better known and more widely used substances would yield much more extensive records.

Number	Subject	PHENYL MUSTARD OIL
17.437	Title	Course of addition of sodium enol alkylmalonic ester to phenyl isothiocyanate
	Author	JOHN ROSS
	Reference	**27.** 1933—p. 5065. *Am. Chem. Abstracts*

J. Am. Chem. Soc., **55,** 3672–3677 (1933).—Na enol malonate and PhNCS give quantitatively the thioanilide of Et methanetricarboxylate, m. 60° (Michael, *J. prakt. Chem.*, **35,** 450 (1887)); MeI gives the *S-Me ether*, m. 58°; the ether is hydrolysed by HCl but not by EtONa. Na enol methylmalonate and PhNCS give only 12 per cent. of ***monothioanilide of tri-Et ethane-α, α, α-tricarboxylate***, pale yellow, m. 92°; 10 per cent. KOH gives the *monothioanilide of methylmalonic acid*, m. 118° and giving thiopropionic anilide. The Na compd. of $NCCH_2CO_2Me$ and PhNCS give almost quantitatively the ***monothioanilide of Me cyanomalonate***, m. 135° (decompn.); the *S-Me* ether m. 83°; $MeCH(CN)CO_2Me$ gives only 10 per cent. of the *monothioanilide of α-cyanopropionic* ***acid***, m. 126°. A modification of the theory of the mechanism of this addn. reaction is consequently necessitated and an explanation is offered.

C. J. WEST.

APPENDIX

LIST OF ABBREVIATIONS, ETC., USED IN ABSTRACTS

ABSOLUTE	abs.
alternating current	a.c.
ampere	amp.
Angström unit	A.
anhydrous	anhyd.
approximat-e, -ly	approx.
aqueous	aq.
Assignor in patent titles	Assr.
Assignee only	Assee.
atmosphere, -es, -ic	atm.
atomic	at.
atomic weight	at. wt.
boiling point	b. p.
British thermal unit	B.Th.U.
calculated	calc.
Calorie (large)	kg.-cal.
calorie (small)	g.-cal.
candle power	c.p.
centimetre	cm.
cerebrospinal fluid	c.s.f.
coefficient	coeff.
concentrated	conc.
concentration	concn.
constant	const.
corrected	corr.
critical	crit.
crystalline	cryst.
crystallised (adjective only)	
cubic centimetre(s)	c.c.
cubic metre(s)	cu. m.
current density	c.d.
decimetre(s)	dm.
decompos-ing, -ition	decomp.
density	ρ, *d*
dilute	dil.
direct current	d.c.
electrocardiogram	e.c.g.
electromotive force	e.m.f.
electron-volt(s)	e.v.
equivalent	equiv.
feet, foot	ft.
for example	*e.g.*
freezing point	f.p.
gallon(s)	gal.
gram(s)	g.
horse power	h.p.
hour(s)	hr.
hydrogen-ion concentration	[H·]
inch(es)	in.
inorganic	inorg.
insoluble	insol.
kilogram(s)	kg.
kilovolt(s)	kv.
kilowatt(s)	kw.
litre(s)	l.
maximum	max.
melting point	m.p.
metre(s)	m.
micron(s)	μ
milliampere(s)	ma.
milligram(s)	mg.
millilitre(s)	ml.
millimetre(s)	mm.
millivolt(s)	mv.
minimum	min.
minute(s)	min.
molecul-e, -ar	mol.
molecular weight	mol. wt.

LIST OF ABBREVIATIONS, ETC., USED IN ABSTRACTS—(*continued*).

namely	viz.	saponification value	sap. val.
normal	N.	second(s) (time only)	sec.
number	no.	* secondary	*sec.*
organic	org.	soluble	sol.
parts per million	p.p.m.	specific	sp.
per cent.	°/₀.	specific gravity	sp. gr.
potential difference	p.d.	square centimetre(s)	sq. cm.
precipitate	ppt.	temperature(s)	temp.
precipitated	pptd.	* tertiary	*tert.*
precipitating	pptg.	vacuum	vac.
precipitation	pptn.	value	val.
preparation	prep.	vapour density	v.d.
qualitative	qual.	vapour pressure	v.p.
quantitative	quant.	viscosity	η.
recrystallised	recryst.	volt(s)	v.
refractive index	*n*.	volume	vol.
relative humidity	R.H.	watt(s)	w.
respiratory quotient	R.Q.	wave-length	λ.
revolutions per minute	r.p.m.	weight	wt.
Roentgen unit	r.		

* The abbreviations for secondary and tertiary are used only in connection with organic compounds.

In addition, elements, groups, and easily recognised substances are denoted in the text by symbols and formulæ. The groups are as follows: methyl, Me; ethyl, Et; *n*-propyl, Pr^{α}; *iso*propyl, Pr^{β}; *n*-butyl, Bu^{α}; *iso*butyl, Bu^{β}; *tert.*-butyl, Bu^{γ}; phenyl, Ph; acetyl ($CH_3 . CO$), Ac; benzoyl ($C_6H_5 . CO$), Bz. (In Section A, III this applies only to inorganic compounds, excluding water, and to chloroform and carbon tetrachloride.) "Oleum" is allowed to describe fuming sulphuric acid and "room temp." for "the ordinary temperature". The symbol for 10 Å. is mμ (not $\mu\mu$) and for the International X-ray unit it is X, not XU. The symbol for 10^{-6} g. is μg (not γ).

The following symbols are used in Section A, III: $>$, greater than; $\gg$, much greater than; $\ngtr$, not greater than (and $<$, $\ll$, $\nless$ conversely); $\propto$, (is) proportional to; $\sim$, of the order of, or approximately.

The principal Pharmacopœias are denoted by B.P., U.S.P., and D.A.B., followed in each case by the identifying numeral.

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CHAPTER II

NOMENCLATURE

> "Too long has this science been burdened and obscured by cryptic words and pompous phrases. Uncouth and barbarous terms must be banished for ever."
>
> —LAVOISIER (after Jaffé).

Names given to organic compounds during the early development of the science either indicated their source, as in—

Indigo.	Lat. ' indicum ' = ' the Indian [substance] '.
Aniline.	Portuguese ' anil ', from the Arabic ' al-nil ' meaning ' indigo '.
Uric acid.	From ' urine '.
Theobromine.	' Theobroma cacao ' (the systematic name of the cacao tree).
Papaverine.	' Papaver somniferum ' (a name used for the opium poppy.)
Alizarin.	Late Greek ' ῥιζάρι ' (cf. Levant ; ' alizari ' for ' madder ').
Menthol.	' Mentha piperitæ ' = ' the peppermint '.
Anthracene.	Greek ' ἄνθραξ ' = ' coal '.

or made reference to some outstanding property, as in—

Fluorescein.	' The fluorescent one '.
Fulvene.	Lat. ' fulvus ' = ' tawny ', or ' orange-yellow '.
Fulminic acid.	Lat. ' fulmen ', ' fulminis ' = ' a thunderbolt or irresistible power '.
Cyanogen.	Greek ' κύανος ' = ' blue ', and ' γεννάω ' = ' to produce '.
Glycol and Glucose.	Greek ' γλυκυς ' = ' sweet '.

The great number of synthetic organic compounds available to-day would make this method impossible.

Approved names of organic compounds are sharply divided into two types—short ' trivial ' names for compounds in every-day use, and systematic nomenclature used in such a way that the name is a complete key to the structure ; there is a gradually diminishing third group of ' semi-systematic ' names, which, although simple, cause confusion, e.g. *m*-nitro-*p*-toluidine. Invention of trivial names is now almost obsolete, but earlier chemists have left a legacy of such names, dating from days when the constitution of organic compounds was entirely unknown or only vaguely surmised. Such names form the foundation on which the structure of systematic nomenclature has been raised. Apart from the question of expediency, trivial names may have a misleading tendency ; carbolic acid and uric acid, for example, retain the " acid " nomenclature now usually reserved for carboxylic compounds ; theobromine contains no bromine, fluorene has no relation to fluorine ; there is no relation between pyrene and pyran. Fortunately, such cases are comparatively rare. On the other hand, some brief cognomen is essential where many complex organic chemicals are used in an industrial organisation, for use by those workmen and executives whose duties involve a constant oral reference to the compounds. It is better to use initials, e.g. ' T.N.T.' for trinitrotoluene, ' T.N.B.A.' for trinitrobenzoic acid, ' D.M.S.' for dimethyl sulphate, ' P.C.M.X.' for parachlorometaxylenol where possible, although it must be admitted that this practice does not wholly solve the problem, and workmen will coin their own names which sometimes find their way back into the whole industry, being aptly chosen and clearly defined. Thus, one intermediate, in a well-known works, was called by the men 'lemonoic acid' because it was pale yellow in colour.

This need has, indeed, always been recognised and as an introduction to the subject of systematic nomenclature one cannot do better than quote the first paragraph of Foster 'On Chemical Nomenclature' (1865) :—

> "In forming a nomenclature for any science, two distinct requirements must be kept in view as having each to be supplied. In the first place, a convenient general language must be provided, to serve as a medium for the ordinary every-day transactions of the science; and in the second place, there must be what may be called the legal language of the science—a language whose terms are, as far as possible, strictly defined, and have an exact and generally recognised value. It is this second stricter language which constitutes the more technical part of scientific nomenclature, and it is this alone which it is either desirable or possible to alter or reform in accordance with any particular state of scientific opinion. The general language of a science will always, in the main, take care of itself; and at any given period it usually contains a large admixture of terms—once technical, but now no longer used for purposes of accuracy—which, like fossils in a rock, tell of the successive changes by which the existing state of things has been brought about. The more strictly technical language, on the other hand, is always formed with more or less premeditation, and is therefore, to a corresponding extent, under control and capable of being reformed. The existence of such a language and its preservation in the highest possible state of efficiency are of the utmost scientific importance; for, although none but a pedant would in all cases employ it (when the use of more popular expressions could lead to no ambiguity), it is quite certain that accurate language is an essential instrument of accurate thought, and that the progress of any science will be greatly retarded unless its language is such as to admit of its facts and theories being stated with any required degree of precision."

In a manual of this size, the minute details of systematic nomenclature cannot be described; but the student is recommended to familiarise himself with the general principles set out below.

The older 'theory of types' marked the introduction of a systematic nomenclature, traces of which are still to be found, as in Kolbe's use of the 'carbinol' nomenclature. Later, development of organic chemistry produced so great a number of substances, that the use of trivial names became impossible. Indeed, Gmelin and Gerhardt proposed to abandon existing nomenclature and to substitute one more capable of systematic manipulation. That of Gerhardt, as outlined in his *Précis de Chimie Organique*, involved many assumptions concerning the structure of organic substances, and was entirely impractical. Gmelin, however, invented new names for all compounds (organic and inorganic) known to him.

"Thus for example :—

1 atom of oxygen is expressed by the word	*ane*,
2 atoms	*ene*,
3 atoms	*ine*,
4 atoms	*one*,
5 atoms	*une*,
6 atoms	*aene*;

and so on.

1 atom of hydrogen is called	*ale*,
2 atoms, by inflexions of the like description.	
1 atom of carbon is called	*ase*,

1 atom of sulphur	*afe,*
—— of nitrogen	*ate,*
—— of chlorine	*ake,*
—— of potass	*pate,*
—— of soda	*mate ;*

> and so with others. Water will be designated by two syllables, derived from its two constituents, and is therefore called *alan ;* sulphurous acid *afen ;* sulphuric acid *afin ;* sulphate of soda, therefore, will be *natan-afin.* Arbitrary names are attached to the compound radicals : thus ethyl is *vine ;* amyl is *myl ;* phenyl is *fune,* etc."

It is not surprising that such a nomenclature was not accepted.

The International Chemical Congress in 1889 appointed a special commission to investigate the situation ; this commission reported at Geneva in 1892, and its recommendations are what is now called the 'Geneva system'. Of the vast array of problems before the Geneva commission, only a few were resolved ; indeed, it may be said that the original Geneva system covers only the aliphatic compounds of simple function, and these not entirely satisfactorily, since it is by no means agreed that the basic principle of searching for the longest carbon chain as the stem for nomenclature is the most satisfactory means of dealing with poly-functional compounds.[1]

After many delays, the International Union of Chemistry again tackled the question of nomenclature, and after several conferences (Varsovie, 1927 ; The Hague, 1928) produced a report at Liège in 1930. It is this report, premature and incomplete, which gives us our present system—'the Liège nomenclature'. Much of the difficulty was due to the almost impossible task which was presented, that of reconciling the usages of *Chemical Abstracts* with those of *Zentralblatt* and the fourth edition of Beilstein's *Handbuch.*

A translation of the important 'Liège report' is given in Appendix I to this chapter. In the remarks on nomenclature which follow, the author has not attempted rigid adherence to the Liège system where current accepted usage conflicts.

Hydrocarbon Nomenclature

In nearly all cases, it is usual to refer the compound either wholly, or by individual groups, to the hydrocarbon from which it is derived ; hence, ability to name any hydrocarbon is the first requisite in naming a compound. All saturated acyclic hydrocarbons are members of the paraffin series (Table I), the trivial names of the first four members of which have become established by custom. From pentane onwards, Greek enumerating prefixes coupled with the termination "*-ane*" serve to constitute names for higher hydrocarbons. Thus, the names of all members of the series end in "*-ane*". Another system is required for dealing with isomerism in the higher hydrocarbons :—

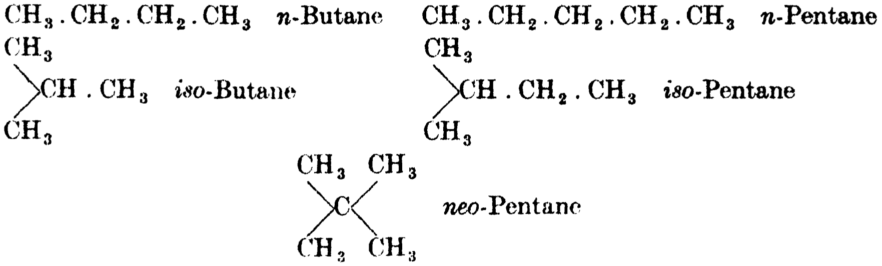
TABLE I

Methane	CH_4	Decane	$C_{10}H_{22}$
Ethane	C_2H_6	Undecane	$C_{11}H_{24}$
Propane	C_3H_8	Dodecane	$C_{12}H_{26}$
Butane	C_4H_{10}	. . .	. . .
Pentane	C_5H_{12}	Eicosane	$C_{20}H_{42}$
Hexane	C_6H_{14}	Heneicosane	$C_{21}H_{44}$
Heptane	C_7H_{16}	Docosane	$C_{22}H_{46}$
Octane	C_8H_{18}	Triacontane	$C_{30}H_{62}$
Nonane	C_9H_{20}		

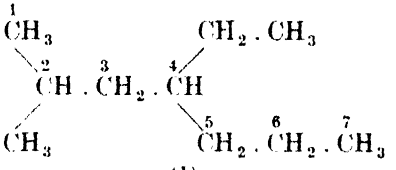
---

[1] See A. Combes (Wurtz, *Dictionary of Chemistry,* 2nd Supplement, 1894, p. 1073) for a full account of this.

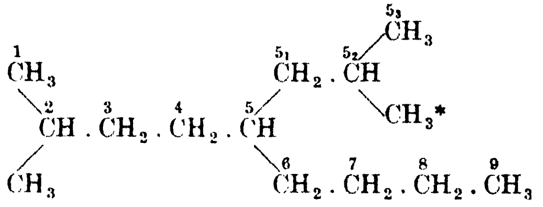
while such isomerism is confined to two or three isomers, the simple prefixes "*iso-*", "*sec-*", "*ter-*" and "*neo-*" are sufficient as in


CH3.CH2.CH2.CH3 n-Butane
CH3.CH2.CH2.CH2.CH3 n-Pentane
CH3 CH.CH3 CH3 iso-Butane
CH3 CH.CH2.CH3 CH3 iso-Pentane
CH3 CH3 C CH3 CH3 neo-Pentane

With higher members, where an increased number of carbon atoms brings an increasingly large number of isomers, a more definite system becomes necessary. In each case the generic title (e.g. "decane") is reserved for the normal hydrocarbon; all other cases are regarded as derivatives of the hydrocarbon which constitutes the longest carbon chain. Thus (1) is regarded as a derivative of heptane, the position of substituent groups being indicated by numbers;



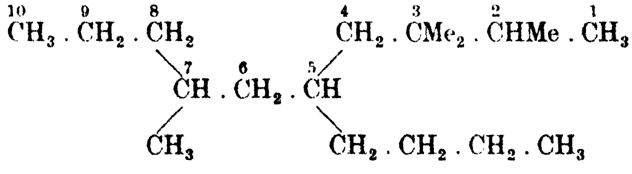
(1)



(2)

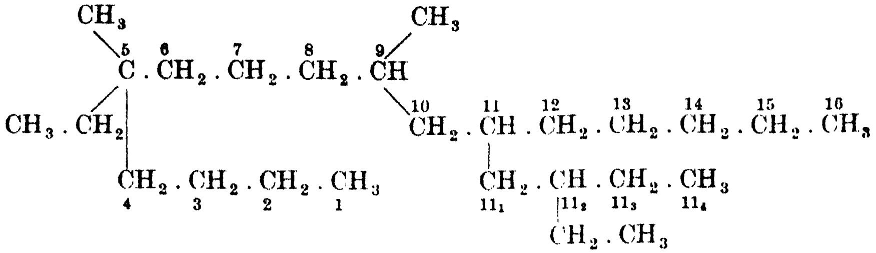
its correct name is "2-methyl-4-ethyl heptane"; as with all truly systematic names the formula of the compound can be deduced from the name. (For direction of stem enumeration, see below).

Additional complications arise, if the substituent groups consist of branched chains, as in (2). Where there are two chains of equal length, that containing most substituent groups is taken as the stem, e.g.



"2, 3, 3, 7-tetramethyl-5-butyl decane"

Using the system already explained, it is clear that the compound (2) is "2-methyl-5-*something* nonane". How is "*something*" to be defined? According to the rigid system the side-chain is dealt with according to the following procedure. The longest carbon chain of the substituent group is numbered outward from the parent chain, using affices 5_1, 5_2, 5_3, etc. The substituent marked (*) in (2) is then regarded as a methyl group substituted into the 5_2 position of the 5-propyl side-chain. To avoid confusion with other groups of the same name, radicles following an affixed numeral sometimes have their terminal "yl" changed to "o"; e.g. "methyl", "ethyl" and "propyl" become "metho", "etho" and "propo". Thus, (2) is "2-methyl-5_2-metho-5-propyl nonane".



(3)

Another example (3) is " 5, 9-dimethyl-5-ethyl-11_2-etho-11-butyl hexadecane ". This system is satisfactory for all saturated aliphatic compounds likely to be met with. It should be noted that in citing the substituents they are arranged in order of increasing size.

UNSATURATED HYDROCARBONS

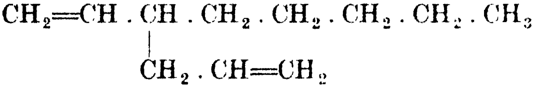
Unsaturation leads to further complications and may be contemplated in two forms :—

(*a*) the presence of one or more double or triple bonds,
(*b*) cyclic structure,

while a combination of all types is not uncommon. A single double bond in a normal hydrocarbon is signified by the change of name from " -ane " to " -ylene " or " ene " ; two double bonds by the change from " -ane " to " -adiene " ; three, to " atriene ". Only in initial cases does this completely describe the compound, since the *position* of the double bond has also to be specified. In (4) below, the double bond lies between the third and fourth carbon atoms ; this is written " heptene-3 " (sometimes " Δ^3-heptene " or " hepta-3-ene "). Applying this process to (5) we get " octadiene-3, 5 "[1]

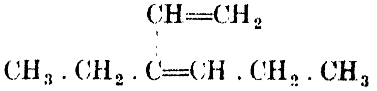
$CH_3 . CH_2 . CH{=}CH . CH_2 . CH_3$ (4)

$CH_3 . CH_2 . CH{=}CH . CH{=}CH . CH_2 . CH_3$ (5)



$CH_2{=}CH . CH(CH_2 . CH{=}CH_2) . CH_2 . CH_2 . CH_2 . CH_2 . CH_3$

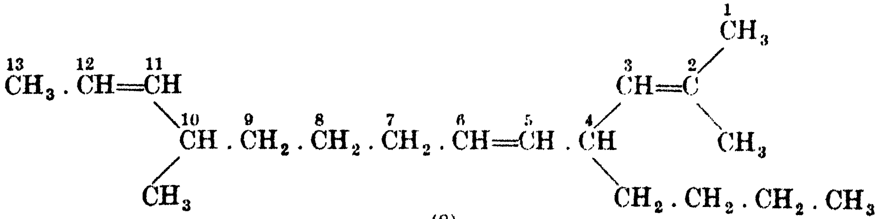
(6)



$CH_3 . CH_2 . C(CH{=}CH_2){=}CH . CH_2 . CH_3$

(7)

(written also, " 3, 5-octadiene ", or " $\Delta^{3,\,5}$-octadiene "). Older literature occasionally signifies the positions of the double bonds by the letters of the Greek alphabet, the compounds (4) and (5) being " γ-heptene " and " γ : ε-octadiene ". An alteration in the method of choosing the stem may be used with unsaturated compounds, the stem being chosen to contain the greatest possible number of unsaturated links. Thus, (6) is " 3-pentylhexadiene-1 : 5 " ; (7) is " 3-ethylhexadiene-1, 3 ", and the more complicated instance (8) is



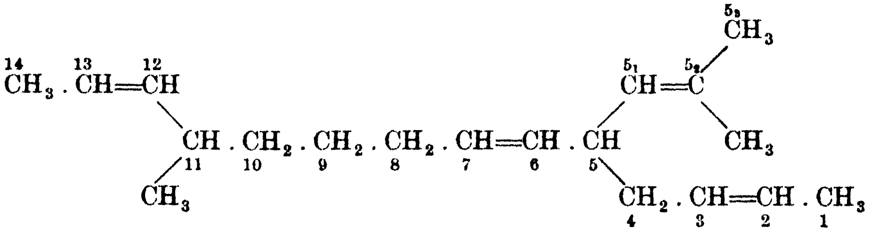
(8)

" 2, 10-dimethyl-4-butyl tridecatriene-2, 5, 11 "

---

[1] It is convenient to place the enumerating figures *before* prefixes and *after* suffixes, e.g. " 3-methyl . . . ", " 6-propyl . . . " but " . . . diene-3, 5 " or " . . . triene-4, 6, 9 ".

Note that the longest carbon chain (that of fourteen) is not chosen. If, however, an additional unsaturated link had been present (as in (9)) the longer



(9)

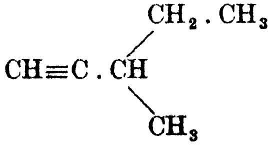
chain could have been chosen, the name being " 11-methyl-5_2-metho-5- (propa-5_1-enyl)tetradecatriene-2, 6, 12 ", although " 2, 10-dimethyl-4(buta-4_2-enyl)-tridecatriene-2, 5, 11 " is shorter and conforms better to the rule given in the following paragraph.

It will be observed that in the examples (8) and (9) the enumeration is from right to left ; this is in order to comply with the rule that the sum total of all substituent numbers shall be as small as possible, e.g. had example (8) been numbered from left to right it would have been named " 4, 12-dimethyl-10-butyltridecatriene-2, 8, 11", an enumeration total of $4 + 12 + 10 + 2 + 8 + 11 = 47$, instead of $2 + 10 + 4 + 2 + 5 + 11 = 34$. This rule is general in all forms of nomenclature.

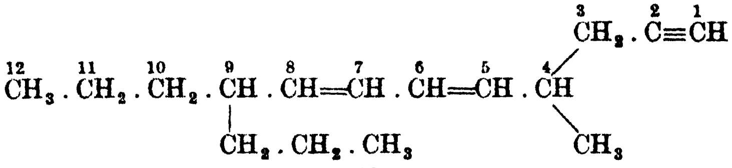
Procedure in the case of substances containing triple bonds is exactly similar, save that the termination " yne " replaces " ene ". Thus, (10) is " pentyne-1 " (more usually called " *n*-propylacetylene ") ; (11) is " 3-methyl-pentyne-1 ". Where both double and triple bonds are present in the same compound (in practice, a very rare matter) both are specified in the termination,

$CH_3 . CH_2 . CH_2 . C{\equiv}CH$

(10)



(11)

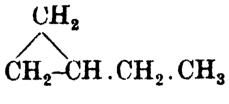


(12)

the double bond taking precedence, thus the systematic name of (12) would be " 4-methyl-9-propyldodecadienyne-5, 7, 1 ".

HOMOCYCLIC COMPOUNDS

Names of hydrocarbons containing ring systems are often referred for nomenclature to the ring, or, in the case of more than one ring, to the largest ring. This rule is not always adhered to, since some rings have accepted trivial names (e.g. benzene), and in others the ring system is treated as a substituent. A few examples will make this clear.



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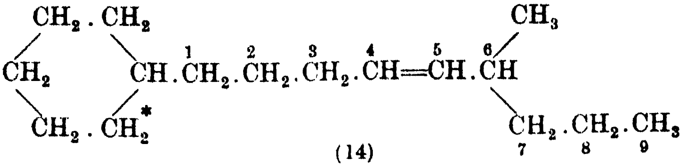

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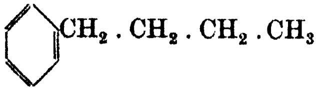

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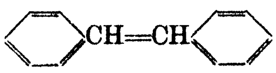

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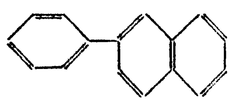

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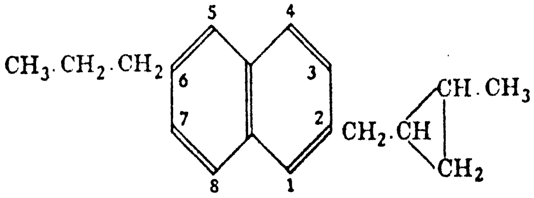
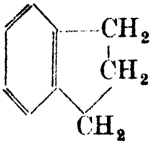


(18)



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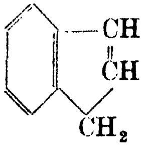

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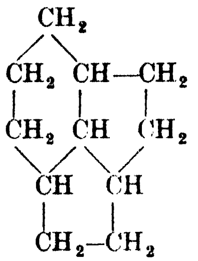


(21)

(13) Alternative names for this substance would be "ethyl-*cyclo*propane" and "*cyclo*propyl ethane" according as the ring is regarded as substituent or as central group; the proposal to regard the substance as "1, 3-*cyclo*pentane" is not often used, in spite of certain advantages. (See Ex. 21.)

(14) The simplest way with this compound is to treat the cyclic group as a substituent; thus, "6-methyl-1-*cyclo*hexylnonene-4", unless the system mentioned in Ex. 13 above, is adopted, i.e., to relate the compound to the open chain hydrocarbon, obtained by opening the ring at *; its name would then be "12-methyl-1, 6-*cyclo*pentadecene-10".

(15) Systematically this compound has been called "1-phenyl butane"; usage has established the name "*n*-butyl benzene".

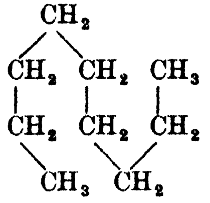
(16) The only name which the older rigid system allows is "1, 2-diphenyl ethene"; the more euphonious "*s*-diphenyl ethylene" is sometimes met with, but the trivial name "stilbene" is most commonly used.

(17) This compound would be known as "2-phenyl naphthalene"; not as "2-naphthyl benzene", the smaller group always being considered the substituent.

(18) This compound presents a case of great interest. If it is regarded as a disubstituted derivative of naphthalene, it becomes almost impossible to enumerate the substituent in the "2" position. In such cases, it is usual to regard the carbon atom (*) as a methane carbon atom, the compound being "2-(6-propyl-naphthyl)-1-(2-methyl-cyclopropyl)-methane". The valuable principle of the methane carbon atom is often used (see "Amines", p. 43).

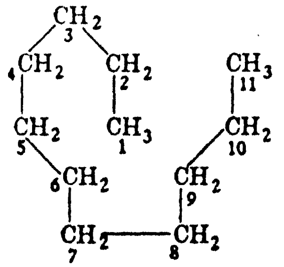
(19) Fused rings often lead to complexities which systematic nomenclature cannot easily overcome without the use of long and cumbrous names. In

many cases, the problem has been solved by creating a trivial name for the fundamental group and using this as the stem for nomenclature of its derivatives. In the case under consideration, there is a clear relation between the compound and indene (20), which leads to the name "hydrindene". The substance is, however, directly related to nonane and might have the systematic



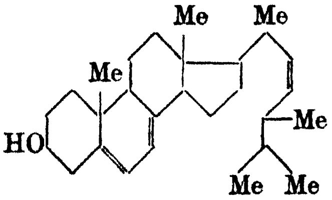
name "bi*cyclo*[4, 3, 0]nonatriene".

(21) At first sight, three rings fused together, as in (21), appear to defy systematic nomenclature. It will be noted that the complexity is to a great extent due to one of the carbon atoms being a member of three rings. No general rule can be given for such cases, which, fortunately, do not often arise; when they do, a suitable trivial name is usually arrived at for the parent ring, although there should be little difficulty in regarding such a substance as a

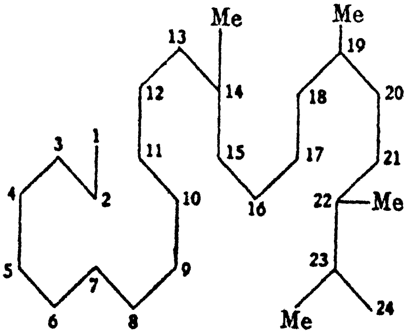


derivative of undecane; it could, therefore, be named "1, 6 : 1, 9 : 2, 11-tri*cyclo*undecane". Ring Index, "tri*cyclo*-[5, 3, 1, 0^{4} ^{10}]undecane".

It is instructive to select a substance such as ergosterol (22) and to ascertain

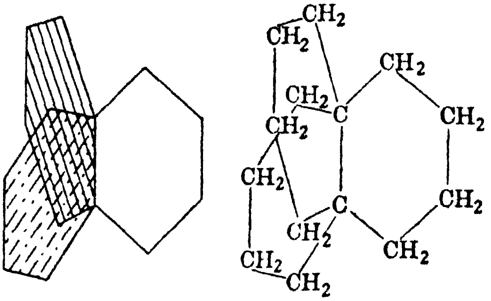


(22)



(23)

whether any systematic method is able to deal with its nomenclature; in the last analysis ergosterol is a derivative of "14, 19, 22, 23-tetramethyl-tetracosane", (23), but would normally be named as a pentamethylhexenyldecahydro*cyclo*pentanophenanthrol. The name is cumbrous, but proves that the system is capable of dealing with an assembly of rings and substituents. It is not suggested that such a name should be used in orally referring to ergosterol, but that it can form a basis of classification of compounds.

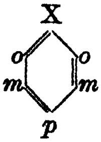


(24)

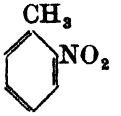
Even with three-dimensional ring-aggregates such as (24) the system does not break down ; (24) could be named “ tri*cyclo*[4, 4, 4, 0]tetradecane ”.

Aromatic Compounds

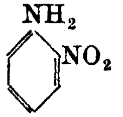
Enumeration of carbon atoms in an aliphatic hydrocarbon stem always takes place from a terminal carbon atom ; enumeration of ring carbon atoms is not so easily defined. With benzene derivatives two methods are in use. Where one substituent only is present, enumeration is unnecessary, benzene being considered as a symmetrical ring ; a second substituent may be considered as ortho-, meta- or para- to the first (25) ; thus, “ *o*-nitrotoluene ” (26) or “ ortho-nitroaniline ” (usually condensed to “ *o*-nitraniline ”) (27). It is to be noted that the two compounds just specified would not be known as “ *o*-methylnitrobenzene ”, or “ *o*-aminonitrobenzene ”. In substituted aromatic nuclei, substituents are arranged in the following order, Cl, Br, I, F, NO_2, NO, NH_2, NH, OH, CHO, CO, CN, NCS, COOH, O . COR, OR, COR, R, H (where R is an alkyl or aryl group). Further, the numbers should be so chosen as to add up to the smallest possible total : “ 1, 2, 4-trinitrobenzene ”, not “ 1, 3, 4-trinitrobenzene ”. Thus, a compound with a methyl group is always considered to have such a group in the position “ 1 ”, and other substituents are referred to this group. Next in order come the larger alkyl, oxy, amino, nitro and halogen substituents ; as an example, compound (28) is a chloronitroaminotoluene, and is not referred to as a methylaminonitrochlorobenzene. It may be much simpler to number round the ring, taking the first substituent as “ 1 ”, proceeding to “ 6 ” (29). As with aliphatic stem enumeration, the route for numbering the ring is chosen so that the sum of the enumerators of substituent groups is a minimum. Compound (30) is called “ 3, 5-dinitrotoluene ” (not “ 5-methyl-1, 3-dinitrobenzene ”) ; (31) is “ 4-chloro-2, 5-dinitroaniline ”. When a disubstituted benzene derivative has a trivial name, names of compounds obtained



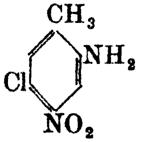
(25)



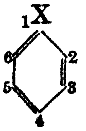
(26)



(27)



(28)



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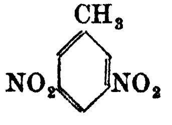
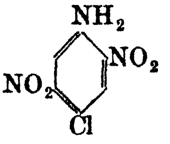


(30)



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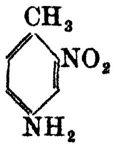
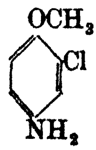
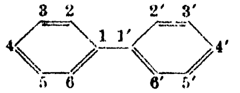


(32)

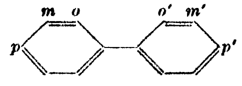


(33)

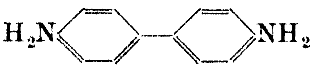
by introduction of a third substituent may be ambiguous unless the numerical system is used. Thus, (32) is " 2-nitro-4-amino toluene ", but from its relation to *p*-toluidine is often called " *o*-nitro-*p*-toluidine ". The latter name is ambiguous, unless one remembers that in naming derivatives of a disubstituted benzene, produced by the introduction of a third group, the position of the latter is taken relative to the group standing first in the order of precedence. " *m*-nitro-*o*-toluidine " is ambiguous in spite of the rule mentioned, since it may refer to " 3-nitro-2-aminotoluene " or " 5-nitro-2-aminotoluene ". Another ambiguous case is the compound often referred to as " *o*-chloro-*p*-anisidine " (33) ; the difficulty lies in remembering which group the chlorine is ortho to ; it is a saving of time and thought, even if a little more costly to print, to call the substance " 2-chloro-4-aminoanisole ". No mention has been made of the system by which benzene itself is named as " *cyclo*hexatriene-1, 3, 5 ", toluene being " 1, 6-*cyclo*heptatriene-1, 3, 5 " and *o*-xylene, " 2, 7-*cyclo*-octatriene-2, 4, 6 ", as the method is seldom used.



(34)



(35)



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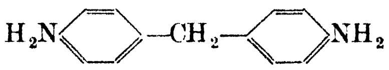
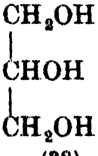


(37)

When two or more aromatic rings are present in the same compound, procedure depends on the circumstances. Two rings joined as in diphenyl (34) are best enumerated from the point of juncture, using " 1′ ", " 2′ ", " 3′ ", etc., for the second ring. The system of (35) is often used for simple derivatives ; thus " *p*, *p*′-diaminodiphenyl " (36), more usually " benzidine ", and " *p*, *p*′-diaminodiphenylmethane " (37), seldom referred to in any other way.

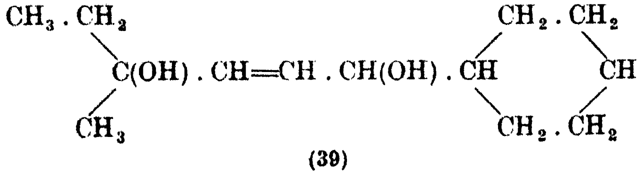
FUNCTIONAL GROUPS

A functional group may be signified either by a suitable prefix as, for example, in " aminobenzene ", or by a systematic modification of the name of the hydrocarbon from which the compound is derived. The latter method cannot be used in certain cases (e.g. ethers, or sulphides) where the functional group serves to join two hydrocarbon residues. It must also be remembered that the International System does not always correspond with common laboratory usage. Oxygen in functional groups leads to the groups —OH, —CHO, —C . CO . C—, —COOH or combinations of such groups. One or more hydroxyl groups are signified by the addition of the affix " -ol ", with a numerical prefix to show the number of such groups, e.g. " di-ol " or " tri-ol ". Position is signified numerically. Thus, $C_2H_5 . OH$ is " ethane-ol " (more usually contracted to " ethanol ") ; glycerol is " propanetriol-1, 2, 3 " (38). The majority of alcohols are known by trivial names, and the system referred to is only used for compounds of multiple function, as, for example, " 4-methyl-1-*cyclo*hexylhexene-2-diol-1, 4 " (39).



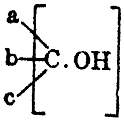
$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

(38)



(39)

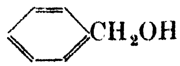
An explanation of the term "carbinol" for the nomenclature of complex secondary and tertiary alcohols is necessary. Every alcohol may be regarded



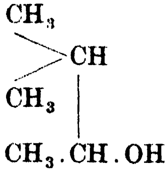
(40)

$CH_3 . CH_2OH$

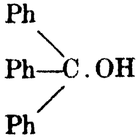
(41)



(42)

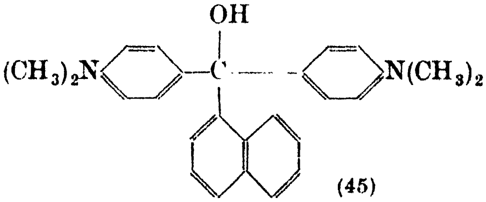


(43)



(44)

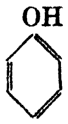
as a derivative of methyl alcohol, of the general type (40). As such it must contain the carbinol group, marked [ ] in (40). Thus, ethanol is "methyl carbinol" (41); benzyl alcohol is "phenyl carbinol" (42); (43) is "methyl isopropyl carbinol"; systematically "3-methyl-butanol-2"; and (44) is "triphenyl carbinol". This method is particularly valuable in cases when three



(45)

complex groups are attached to one carbon atom, as in (45), "bis-(4-dimethyl-aminophenyl)-1-naphthyl carbinol". This compound also illustrates the use of "bis-" to signify duplication of the complex group bracketed after its use. "Tris" and "tetrakis" signify triplication or quadruplication of the bracketed group succeeding.

There are two distinct ways of regarding aromatic hydroxy compounds in which the hydroxyl group is directly attached to the nucleus. The simplest compound (46) is always referred to as "phenol", although the older name "carbolic acid" still survives in commerce. The substituted derivatives of phenol may be referred to as such, or as hydroxy derivatives of the hydrocarbon. Thus, (47) is "4-hydroxytoluene", "*4-hydroxy-1-methyl benzene*", or "4-methyl phenol"; the true systematic name is shown in italics, but the compound is more usually called "para-cresol". With fused ring compounds, the same rule applies; (48) is "8-hydroxy-1-methyl naphthalene". In Continental usage the prefix "hydroxy" is often contracted to "oxy", but this is specifically excluded from the Liège convention.



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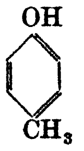

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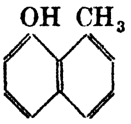


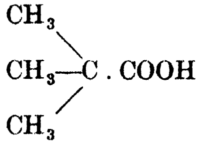
(48)

ALDEHYDES

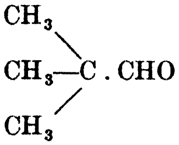
Aldehydes are systematically named from the corresponding hydrocarbon in exactly the same way as alcohols, save that "al" is used as the group termination in place of "ol". As usual, this system is ignored where trivial names have become established by custom. Thus, H . CHO is "methanal", CH_3 . CHO is "ethanal", names rarely used in place of the more usual "formaldehyde" and "acetaldehyde"; in fact, the "al" termination is seldom used, it being customary to name aldehydes from the corresponding acid :—

$CH_3 . CH_2 . CH_2 . CH_2 . COOH$
Valeric acid

$CH_3 . CH_2 . CH_2 . CH_2 . CHO$
Valeraldehyde (Pentanal)

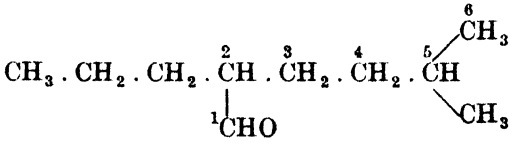


Trimethyl acetic acid



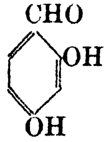
Trimethylacetaldehyde
(2, 2-dimethyl propanal)

It would be a step forward in nomenclature if the " al " terminology for aldehydes was more widely used. The carbon chain of an aldehyde is numbered from the aldehyde group, since the carbon of that group is counted as an integral part of the carbon chain. Thus, (49) is " 5-methyl-2-propylhexanal ",



(49)

and would not be called " 4-aldo-7-methyl octane ". The use of the term " aldo " may have to be adopted in the aromatic series, where, whenever possible, the aldehyde group takes precedence over others, the compound being regarded as a derivative of benzaldehyde. Thus, the compound (50) is " 2, 4-dihydroxybenzaldehyde " ; (51) is " 2-methyl-5-chlorobenzaldehyde ",



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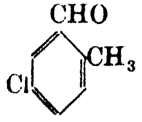

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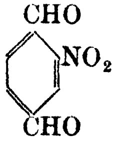

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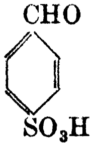
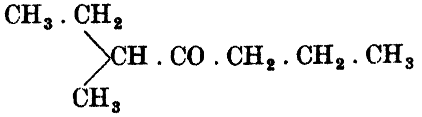


(53)

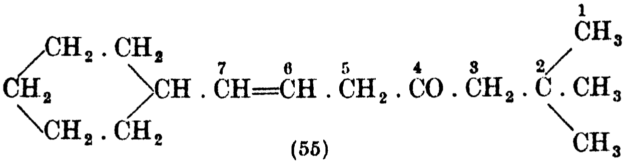
and (52) is " nitroterephthalaldehyde ". It is conceivable that these three compounds might have been named " 1, 3-dihydroxy-6-aldo benzene ", " 2-aldo-4-chloro toluene ", and " 2, 5-dialdo nitrobenzene ", but in practice the use of " aldo " is only the last resort, in instances such as " 4-aldo benzene sulphonic acid ", (53), and even then, " benzaldehyde-4-sulphonic acid ", would be preferred by some chemists.

KETONES

As with aldehydes, systematic nomenclature of ketones differs from that conventionally adopted. The former regards a ketone as a derivative of a hydrocarbon in which one or more methylene groups have been altered to carbonyl groups, a condition signified by the addition of the syllable " one " to the name of the corresponding hydrocarbon. Thus, (54) is " 3-methyl heptanone-4 ", while (55) is " 2, 2-dimethyl-7-*cyclo*hexyl-heptene-6-one-4 ". Conventional nomenclature regards ketones as derived from the structure a—CO—b, and names them by denoting the names of the groups " a " and " b " followed by the word " ketone ". The method is satisfactory for simple ketones, e.g. (56), " methylpropyl ketone ", but complications enter as the groups become more elaborate. Even in (57), " (2-methylamyl)methyl ketone ", brackets must be used to avoid confusing the " methyl " of the side-chain with that adjacent to the carbonyl group. In more complex instances such as (55), " 2, 2-dimethyl-7-*cyclo*hexyl-heptene-6-one-4 ", this method fails entirely. The



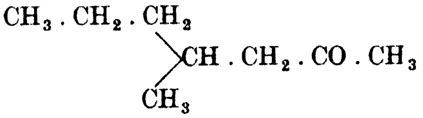
(54)



(55)

$CH_3 . CH_2 . CH_2 . CO . CH_3$

(56)



(57)

systematic method is of further value in compounds of multiple function ; e.g. $CH_3 . CH_2 . CH_2 . CO . CH_2 . CH_2 . CH_2 . CHO$, the systematic name of which is " octanal-1, one-5 ", the more conventional ketone nomenclature breaking down through inability to name the group

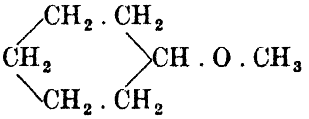
$$—CH_2 . CH_2 . CH_2 . CHO.$$

ETHERS AND ESTERS

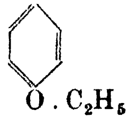
Systematic nomenclature for ethers is at variance with conventional practice. Save for ethers containing the $CH_3O—$ and $C_2H_5O—$ groups which are often called " methoxy " and " ethoxy " compounds, and the phenoxy ($C_6H_5O—$) compounds, ethers have the following conventional nomenclature, viz., to name the groups on either side of the ether oxygen, and to add the word " ether ".

$CH_3 . CH_2 . CH_2 . O . CH_2 . CH_3$

(58)

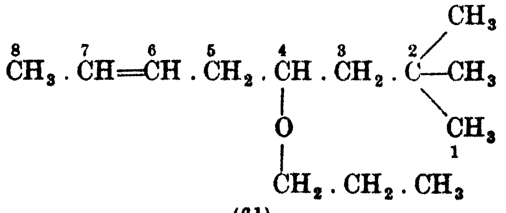


(59)



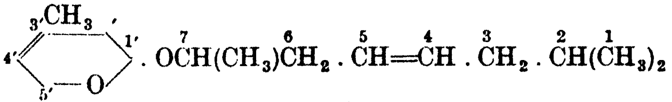
(60)

The method is simple enough with ethers such as (58) " ethyl propyl ether ", " methyl(*cyclo*hexyl)ether " and " ethyl phenyl ether ", (59) and (60). Complex ethers need the use of brackets to avoid confusion between the two sets of groups. Thus, (61) is " 4-(2, 2-dimethyloctene-6)propyl ether ". Many of the



(61)

simple aromatic ethers have trivial names, as " anisole " for " methyl phenyl ether " ; " phenetole " for (60), while one or two are known industrially as " oxides ", e.g. " diphenyl oxide ". Systematically, however, ethers are regarded as alkoxyl derivatives; (58) is "1-ethoxypropane", (61) "2, 2-dimethyl-4-propoxyoctene-6", (60) "ethoxybenzene"; ordinary "ether" is "ethoxyethane". The systematic method has the advantage of being universally applicable, even when both groups attached to the ether oxygen are complex, as in (62), which is

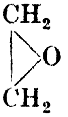


(62)

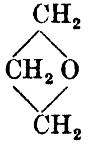
7[3′-methyl-1′, 5′-epoxypentene-3′-oxyl-1′]-2-methyloctene-4.

Ether oxygen often constitutes part of a ring, thus calling for special nomenclature. The simple substances (63) to (65) are conventionally regarded as the oxides of unsaturated hydrocarbons; thus, "ethylene oxide", "propylene oxide", and "butylene oxide".

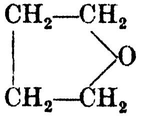
The Liège convention uses the term "epoxy" to indicate ring ethers; (63) is "epoxyethane"; (64) "1, 3-epoxypropane"; (65) "1, 4-epoxybutane" and the substance commonly called "epichlorhydrin" (66) becomes "1, 2-epoxy-3-chloropropane".



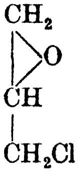
(63)



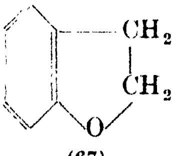
(64)



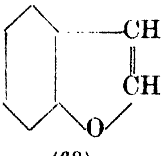
(65)



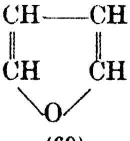
(66)



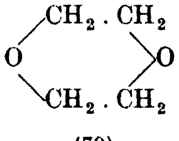
(67)



(68)



(69)

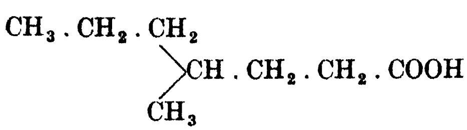


(70)

Complex or unsaturated rings usually have trivial names, not always, unfortunately, in keeping with their chemical character. Thus, "coumarane" (67) is not a saturated hydrocarbon, nor is "coumarone" (68) a ketone; "furane", too, is a misnomer, since it is neither saturated nor is it a hydrocarbon (69); custom has, however, established the usage, but "furan" is now preferred. Note that furan is, systematically, "1, 4-epoxybutadiene-1, 3". (See also Rule 24, Appendix I.) Attention is called to the use of the term "pyran" for the amylene oxide ring. "Pyran" is in no way related to "pyrene", a polycyclic aromatic hydrocarbon described on page 176. No general rules can be given for cases in which two ether oxygen atoms are present in the same ring; the name "dioxane" has been accepted for the compound (70) from ethylene glycol.

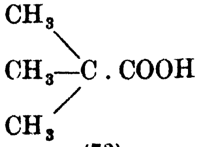
CARBOXYLIC ACIDS

One or more carboxyl groups may be introduced into an organic compound at any point. It is convenient to regard such groups as substituents in aromatic and condensed ring compounds, but in aliphatic compounds, the —COOH group may be regarded as a $—CH_3$ group which has been converted; in this way, the carbon atom of the group is regarded as being part of the parent hydrocarbon. Such carboxyl groups may be signified by the word "acid", or “ -oic acid ”, after the name of the appropriate hydrocarbon; a prefix “ di- ”, “ tri- ”, “ tetra- ”, etc., where necessary, signifies duplication of such groups, and numerical prefixes indicate their positions. Examples are given below :—

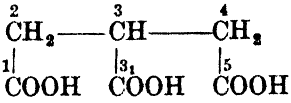


$$\begin{array}{l} CH_3.CH_2.CH_2 \\ \quad > CH.CH_2.CH_2.COOH \\ CH_3 \end{array}$$

(71)



(72)



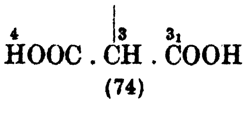
$$\begin{array}{ccc} \overset{2}{CH_2} & \text{——}\overset{3}{CH}\text{——} & \overset{4}{CH_2} \\ {}_1| & |_{3_1} & |_5 \\ COOH & COOH & COOH \end{array}$$

(73)

Systematically, (71) is “ 4-methyl heptane acid-1 ” ; (72) is “ 2, 2-dimethyl propane acid-1 ”, and (73) would be termed “ 3-methylpentanetriacid-1, 3_1, 5 ”. It is most unusual to find acids named in this way, trivial names being common, while in addition, a great many acids are referred to as derivatives of acetic acid. Thus, (72) is commonly called “ trimethyl acetic acid ”, and (73) “ propane tricarboxylic acid ”, or “ tricarballylic acid ”. In general, the trivial name indicates the source from which the acid may be obtained :—

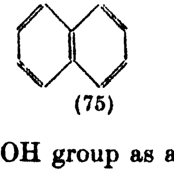
Malic acid.	Lat. “ Malum ” = an apple.
Succinic acid.	Lat. “ Succinum ” = amber.
Acetic acid.	Lat. “ Acetum ” = vinegar.
Stearic acid.	Greek “ στέαρ ” = tallow.
Benzoic acid.	Arabic “ luban jawa ” = incense from Java, through “ benjawn ”, “ benjamin ” and “ benzoin ”.
Oxalic acid.	“ Oxalis acetosella ” (the wood-sorrel).
Tropic acid.	“ Atropa belladonna ” (the deadly nightshade), *via* “ atropine ”.

Attention is drawn to the general habit of making the stem termination of acid names “ -ic ”. The use of the term “ carboxylic acid ” is firmly established, even in ambiguous cases.



$$\begin{array}{l} \overset{1}{HOOC}.\overset{2}{CH}.\overset{2_1}{COOH} \\ \qquad\ \ |_3 \\ \overset{4}{HOOC}.CH.\overset{3_1}{COOH} \end{array}$$

(74)

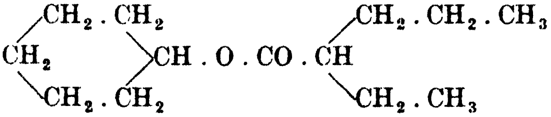


(75)

In this system, instead of regarding the —COOH group as an altered stem carbon atom, the whole group is treated as a substituent. Thus, ethane tetracarboxylic acid is commonly used for (74) where “ 2, 3-dimethyl butanetetracid-1, 2_1, 3_1, 4 ” would be the systematic name. It must be admitted that the systematic nomenclature for acids is a little cumbrous, even if foolproof. The “ carboxylic acid ” system is invariably used for aromatic acids, although the more systematic method could be used. Thus, (75) would seldom be called anything but “ α-naphthoic acid ” or “ naphthalene-1-carboxylic acid ” ; “ 1-methyl naphthalene acid-1 ” is indicated systematically, even if the naphthalene ring is conceded. The use of the latter system is useful in compounds of multiple function.

THE ESTERS

Esters of simple acids may be represented by the generic formula $R_1.CO.O.R_2$, and must have had their origin in an acid $R_1 . COOH$ and an alcohol $R_2 . OH$. The ester is regarded as an alkyl or aryl derivative of the acid, of the " salt " type. Thus, $CH_3 . CO . OC_2H_5$ is " ethyl acetate ", while $C_2H_5 . CO . OCH_3$ is " methyl propionate ". Difficulties arise only when the acid or alcohol is difficult to name; thus (76) is " *cyclo*-hexyl(hexane-3-carboxylate) ". A second method of ester nomenclature is shown in the example " propionyl propyl ester " for $C_2H_5 . CO . OC_3H_7$; it is not recommended, as it becomes unmanageable in all but the simplest cases.

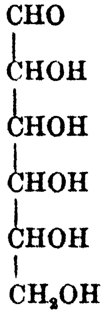


(76)

Esters of inorganic acids are named as salts of such acids, e.g., CH_3I, " methyl iodide "; $(C_2H_5)_2SO_4$ " diethyl sulphate ".

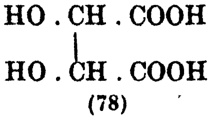
OXYGEN COMPOUNDS OF MULTIPLE FUNCTION

It is not possible to give a set of rules to cover all cases in which several functional groups occur in the same molecule. In general, the compound is referred to the appropriate hydrocarbon skeleton, and each functional group considered in turn. A few examples will make the process clear. The open-chain formula for glucose (77) is " hexanalpenta-ol-2, 3, 4, 5, 6 "; tartaric acid becomes " butanediol-2, 3-diacid-1, 4 " (78); acetone dicarboxylic acid is " pentanone-3-diacid-1, 5 " (79), while systematically maltose (80) could be named " 2-(6-methylpyranyl-tetra-ol-3, 4, 5, 6_1)5′-(6′-methylpyranyl-tetra-ol-2′, 3′, 4′, $6'_1$) ether ", which concedes the pyran ring; more fundamentally it could be called " 4-[1, 5-epoxyhexantetra-ol-2, 3, 4, 6-oxyl-1]-1, 5-epoxyhexantetra-ol-1, 2, 3, 6 "; the latter is to be preferred being shorter and more clearly defined.



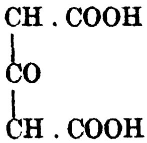
$$\begin{array}{l} \mathrm{CHO} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

(77)



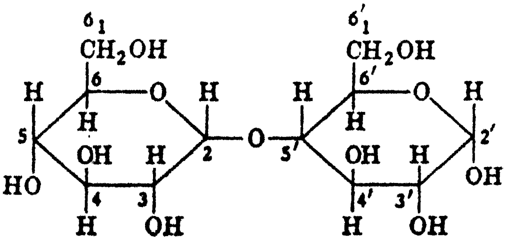
$$\begin{array}{l} \mathrm{HO\,.\,CH\,.\,COOH} \\ \quad\;\;| \\ \mathrm{HO\,.\,CH\,.\,COOH} \end{array}$$

(78)



$$\begin{array}{l} \mathrm{CH\,.\,COOH} \\ | \\ \mathrm{CO} \\ | \\ \mathrm{CH\,.\,COOH} \end{array}$$

(79)

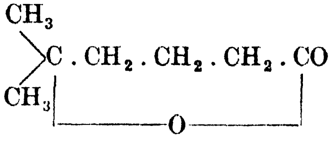


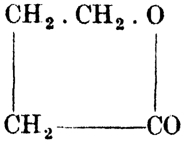
(80)

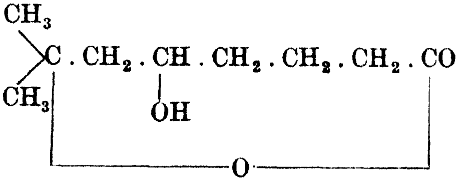
It is only natural that the trivial names should be preferred for general usage, and the systematic method resorted to only in those cases where ambiguity is likely to result, or when the compound is of so little general importance that no trivial name has been attached.

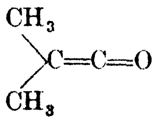
LACTONES, KETONES, ETC.

Lactone names invariably follow those of the corresponding acids, the word "lactone" being added; thus (81) is "2-methyl hexanol-2-acid-6 lactone". Shorter, less systematic, names are sometimes substituted, as in "γ-butyrolactone" (82). The system is satisfactory unless there is more than one hydroxy or carboxyl group in which case the position of the lactone ring is indicated numerically, as in (83) "7-methyl octanediol-5, 7-acid-1-lactone-1, 7" (see also Chap. XV). The alternative method, seldom used, is to regard a lactone as the derivative of a heterocyclic ring system, e.g. "α-pyrone". If the epoxy convention be used the compound (83) becomes "7-methyl-1, 7-epoxyoctanol-5-one-1". The method is simple, but has an unfamiliar appearance; the epoxy convention may be used with all lactones; compound (81) would then become "5-methyl-1, 5-epoxyhexanone-1"; (82), "1, 4-epoxybutanone-1".

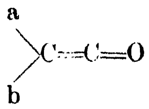

(81)


(82)


(83)


(84)

$(CH_3)_2C{=}C{=}O$


(85)

$(a)(b)C{=}C{=}O$

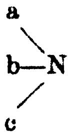
Ketenes are not named systematically; their names are derived from the parent ketene $CH_2{=}C{=}O$, by enumeration of the substituent groups "a" and "b" in (85). System demands that (84) shall be described as "2-methylpropen-1-one-1", (which might, without ambiguity, become "2-methyl-propenone-1"); common usage is, however, "dimethyl ketene". Ozonides, it may be added, are referred to as such, the name of the compound from which they are derived prefixing the term "ozonide"; thus, "dipentene diozonide". Peroxides are treated as substituted hydrogen peroxide compounds.

NITROGENOUS COMPOUNDS

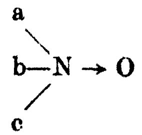
The chief nitrogenous functional groups are summarised in the following scheme:—

Group I

1. Amines

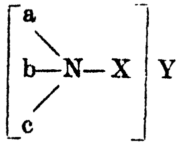


$(a)(b)(c)N$



$(a)(b)(c)N \rightarrow O$

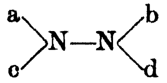
Amine oxides

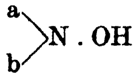


$[(a)(b)(c)N{-}X]\,Y$

Quaternary salts and bases

2. Hydrazines





NH_2OR

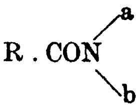
Hydroxylamines

Group II

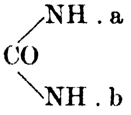
1. Amides

$R.CONH_2$

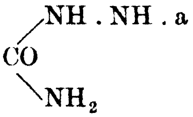
Substituted amides



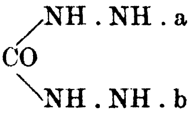
2. Derivatives of carbonic acid



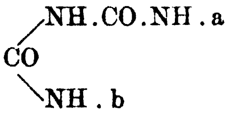
Ureas



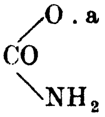
Semicarbazides



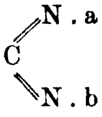
Carbazides



Biurets

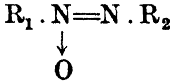


Esters of carbamic acid (Urethanes)



Carbo-di-imides

Group III

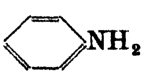
$R.NO_2$	Nitro compounds	$R.CN$	Cyanides (nitriles)
$R.NO$	Nitroso compounds	$R.NC$	*Iso*cyanides (carbylamines)
		$R.ONC$	Fulminates
$R:N.OH$	Oximes	$R.OCN$	Cyanates
$R_1N{=}NR_2$	Azo compounds	$R.NCO$	*Iso*cyanates
$R.CH{=}NH$	Imino compounds	 $R_1.\underset{\overset{\downarrow}{O}}{N}{=}N.R_2$	Azoxy compounds

Group IV

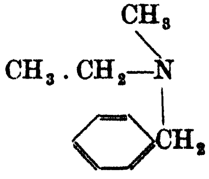
The heterocyclic compounds of nitrogen.

Group I. The Amines and Ammonium Bases

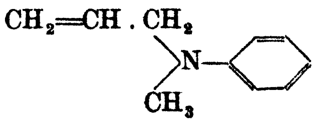
Amines and quaternary bases are regarded for nomenclature as derivatives of ammonia or of an ammonium salt. Thus, CH_3NH_2, $(CH_3)_2NH$ and $(CH_3)_3N$ are "methylamine", "dimethylamine" and "trimethylamine". Nomenclature follows the rule that groups (other than the hydrogen atom) attached to nitrogen are described in order of ascending magnitude, followed by the generic description "amine". Examples are (86) "phenylamine", to which the trivial name "aniline" is often applied; (87) "methylethylbenzylamine", and (88) "methyl-(2-propenyl)-phenylamine" or ("methylallylaniline").



(86)

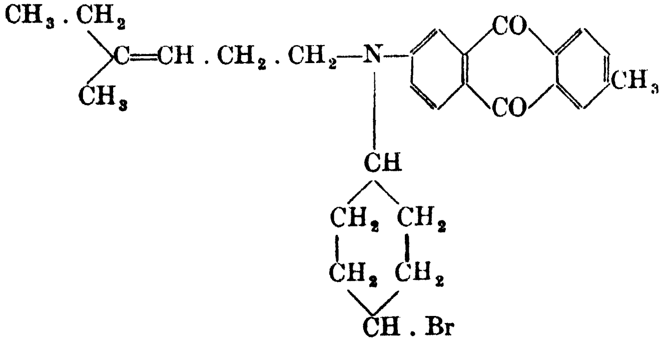


(87)

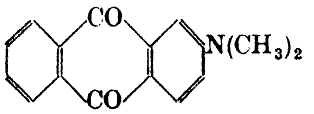


(88)

The method is readily applied to more complex instances; (89) is "1-(4-methylhexenyl-3)-1-(4-bromo*cyclo*hexyl)-2-(6-methyl-anthraquinonyl)amine", conceding trivial names for the ring stems. In many cases, however, the $—NH_2$ group or the NR_1R_2 group must be treated as a substituent. Thus (90) is most simply described as "2-dimethylamino-anthraquinone"; (91) as "7-aminophenanthrene". Trivial names such as "aniline" are often used; thus, (92) is often called "xenylamine", while in many aromatic compounds the amino group is taken as a substituent and is detailed before the methyl, oxy or methoxy groups, when the latter are present. Compound (93), "*p*-toluidine", would be named systematically as "4-amino-1-methyl benzene"; an intermediate form is "*p*-aminotoluene"; (94) has been called many names; the most commonly met with is, unfortunately, "*o*-nitro-*p*-toluidine", to interpret which it is necessary to remember that the methyl is the key group. The full systematic name, "2-nitro-4-amino-1-methylbenzene" is too pedantic for everyday use, but "2-nitro-4-aminotoluene" is convenient and accurate. There is no difficulty in the case of "4-chloro-3-aminopropylbenzene" (95); and while (96) is conveniently known in the laboratory as "2, 4-dichloraniline", its systematic name would be "2, 4-dichloro-1-aminobenzene". In (97) one of the methoxy groups must be taken as "1", the compound becoming "4-chloro-2-nitro-5-amino-1, 3-dimethoxybenzene". This system may be extended to compounds of considerable complexity such, for example, as



(89)



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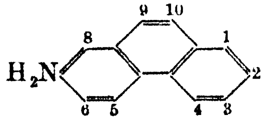

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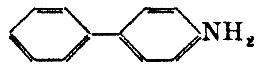

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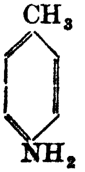

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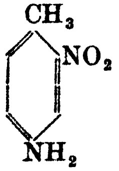

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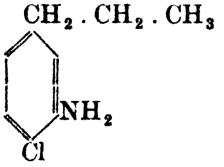

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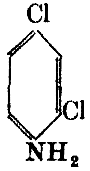

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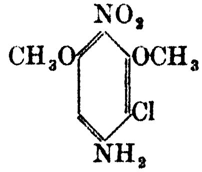
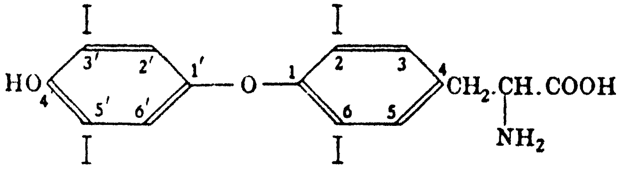


(97)

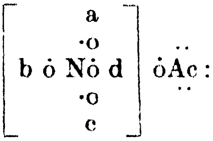
" thyroxine " (98) which treated, in part, systematically is " 2, 3′, 5′, 6-tetraiodo-4_2-amino-4′-hydroxy-4-propyl-1, 1′-diphenyl ether acid-4_3 ".



(98)

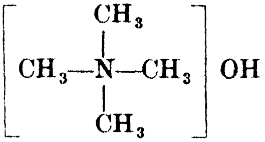
Quaternary Compounds

Since the constitution of quaternary compounds implies one electrovalency, they may be treated for nomenclature as substituted ammonium salts, derived from the general formula (99). Thus (100) is " tetramethyl ammonium hydroxide ", and (101) " trimethyl *cyclo*hexyl ammonium iodide ". Complications ensue when the nitrogen is part of a heterocyclic ring ; in such cases two or three of the nitrogen valencies are attached to the same group. The difficulty is overcome by the use of the " inium " termination as, for example, in (102), which is " methyl pyridinium iodide ", and (103), which is " dimethyl(2-propylpiperidinium)bromide ", or " dimethyl coniinium bromide ".



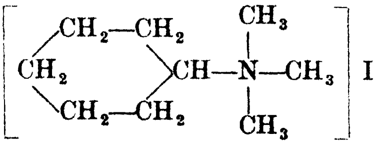
$$\left[\begin{array}{c} a \\ \cdot o \\ b\,\dot{o}\,N\dot{o}\,d \\ \cdot o \\ c \end{array}\right] \ddot{\dot{o}}Ac\ddot{:}$$

(99)



$$\left[\begin{array}{c} CH_3 \\ | \\ CH_3-N-CH_3 \\ | \\ CH_3 \end{array}\right] OH$$

(100)



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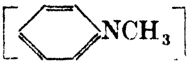
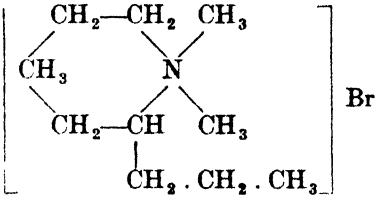
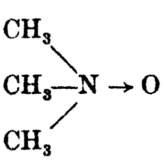


(102)

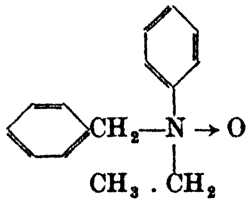


(103)

With amine oxides, the name is obtained by adding " oxide " after the name of the amine. Thus (104) is " trimethylamine oxide ", and (105) " ethylphenylbenzylamine oxide ".



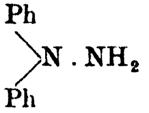
(104)



(105)

Azo, Hydrazo and Azoxy Compounds

Simple derivatives of hydrazine are referred to that substance as a stem. No special indication is required to denote the position of a single substituent, but two substituents may be indicated by the prefixes " *as* " or " *s* " (" asymmetrical " or " symmetrical ") according as two groups are attached to one nitrogen atom, or to each of two such atoms. Although such a system is satisfactory for disubstituted hydrazines, it breaks down in the case of three or more substituents, and it becomes necessary to refer to the two nitrogen atoms of the hydrazine structure as " 1 " or " 2 " respectively. Both methods

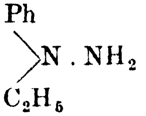


$(Ph)_2N.NH_2$

(106)

$Ph.NH.NH.Ph$

(107)

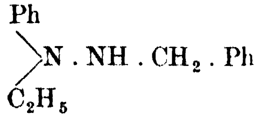


$(Ph)(C_2H_5)N.NH_2$

(108)

$Ph.NH.NH.C_2H_5$

(109)



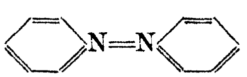
$(Ph)(C_2H_5)N.NH.CH_2.Ph$

(110)

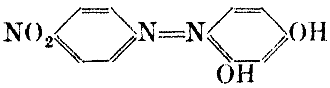
are exemplified in the compounds illustrated above, which are :—

(106) *as*-Diphenyl hydrazine.
(107) *s*-Diphenyl hydrazine. (Commonly called " hydrazobenzene ".)
(108) *as*-Ethyl phenyl hydrazine.
(109) *s*-Ethyl phenyl hydrazine.
(110) 1-Ethyl-1-phenyl-2-benzyl hydrazine.

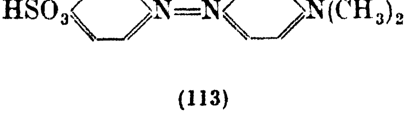
Azo-compounds, containing only one azo link have the general formula a . N=N . b. Nomenclature is confused, but is chiefly related to two systems. Thus (111) is always referred to as " azobenzene ", and many compounds are referred numerically to this compound, e.g. (112), the compound used as a delicate test for the presence of magnesium, may be called " 4′-nitro-2, 4-dihydroxyazobenzene ", while the compound " methyl orange " (113) is " 4-dimethylamino azobenzene-4′-sulphonic acid ". Such a system can only be used when the nuclei on either side of the azo group are identical ; where such groups differ fundamentally, a somewhat unusual method is commonly employed, namely, to name the two groups on either side of the azo-link as they would be, in the absence of such link, coupling the two names with " azo " to indicate the nature of the compound. In the case of the above compounds the names would be :—



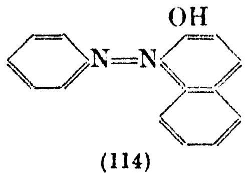
(111)



(112)



(113)



(114)

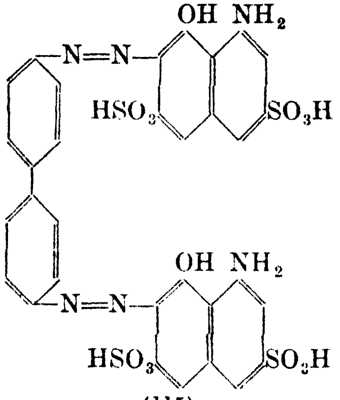
(112) " 4-Nitrobenzene-azo-resorcinol."
(113) " 4-Dimethylaniline-azo-benzene-4-sulphonic acid."
(114) " Benzene-azo-β-naphthol."

These are the common names of these compounds ; inspection shows that they are not always definite, leaving, in some cases, e.g. (112), the point of attachment of the azo group unspecified. Amendment is suggested to :—

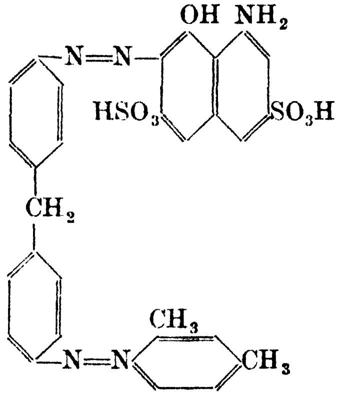
(112) " 4-Nitrobenzene-azo-2, 4-dihydroxybenzene."
(114) " Benzene-azo-1-(2-naphthol),"

the assumption being made that in the benzene ring, attachment of the azo group is always in the " 1 " position.

The latter method is the better, and in spite of its apparently cumbrous nature should be adhered to, since it can be systematically extended to compounds in which more than one azo group occurs. Thus, the dyestuff (115) is " 8-hydroxy-1-aminonaphthalene-3, 6-disulphonic acid-7-azo-4-diphenyl-4′-azo-7-(8-hydroxy-1-aminonaphthalene-3, 6-disulphonic acid) ". The second example would be " 2, 4-dimethylbenzene-azo-4-diphenylmethane-4′-azo-7-(8-hydroxy-1-aminonaphthalene-3, 6-disulphonic acid) ". Fortunately, most of these substances have trivial names.

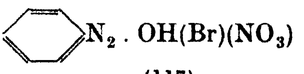


(115)



(116)

Diazonium compounds are regarded as salts of the corresponding diazonium hydroxide. Thus (117) will comprise benzene diazonium hydroxide, bromide, nitrate, etc., while (118) is " 2, 4-dimethyl benzene-diazonium bromide ".



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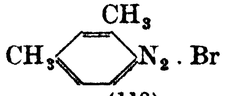

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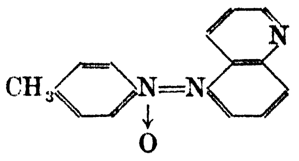

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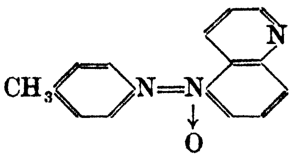


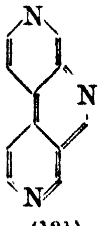
(120)

With azoxy compounds a system similar to that for azo compounds is used, the only difference being that the group first mentioned is held to be adjacent to the nitrogen carrying the oxygen ; thus (119) is " 4-toluene-azoxy-5-quinoline ", while " quinoline-5-azoxy-4-toluene " would have the structure (120).

Other Nitrogenous Compounds

Many other types of nitrogenous compounds are met with in organic chemistry, but do not call for any special consideration from the point of view of nomenclature. Thus, nitro, nitroso and cyano groups are treated as substituents in the majority of cases, while other groups of compounds are, in general, treated as substituted derivatives of a simple parent nucleus. They call for no special principles, and reference will be made to their nomenclature under the appropriate section later.

Heterocyclic Compounds



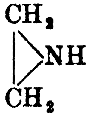
(121)

The Chemical Society of London has used the ring-system nomenclature of Richter's *Lexikon der Kohlenstoffverbindungen*, but this is often found inadequate for modern needs. In general, all heterocyclic substances are referred to some simple ring, the name for which has been accepted; even substances such as (121) are referred to the universally accepted "phenanthrene" and its name becomes "2, 7, 9-triazaphenanthrene". The reader should note the consistent use in modern chemical literature of the syllable "aza" for a hetero-nitrogen atom; "thia" and "oxa" being used for sulphur and oxygen in the same circumstances.

A recent publication (1940) of the Ring Index (see Appendix II) gives an excellent and valuable summary of current practice in ring nomenclature.

Heterocyclic Nitrogen Compounds

For the purposes of this book it is best to consider the heterocyclic nitrogen compounds in five classes, containing three, four, five, six and higher numbers of atoms in the ring. There are three types of three-membered nitrogenous rings :—



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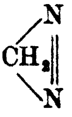

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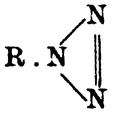
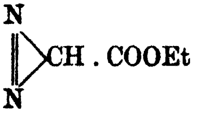


(124)

Formula (122) shows the parent of the simplest class of nitrogen rings, "ethylene-imine"; but few of its derivatives are known. The Liège convention regards 'imine-rings' as 'epamino' compounds, e.g. (122) is "epaminoethane", trimethyleneimine becomes "1, 3-epamino propane", etc., up to piperidine, "1, 5-epaminopentane". Substance (123) is called "diazomethane", from which any substituted derivative may be named. The commonest derivative of this ring is (125), "diazoacetic ester", the name of which indicates the common method of treating the two nitrogen atoms as a substituent diazo group.[1] When the two nitrogen atoms are replaced by two —NH groups, the compound is often termed a "hydrazi" compound, e.g.



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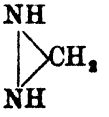

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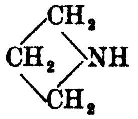

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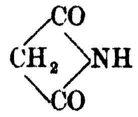

(128)

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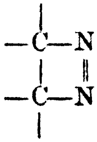
[1] The cyclic formulæ for diazomethane and diazoacetic ester represent a structure which, in modern literature, is usually replaced by resonance formulæ. They are included here because they are frequently encountered in the literature up to 1930.

(126) " hydrazimethane ". Derivatives of the three-nitrogen ring (124) are considered as " azides ", i.e. salts or esters of hydrazoic acid. One general rule may be cited in the case of heterocyclic nitrogen compounds, namely, that substituents on a nitrogen atom are often indicated by " N— ".

FOUR-MEMBERED NITROGENOUS RINGS

" Trimethyleneimine ", or " 1, 3-epaminopropane " (127), the parent of the series, is seldom met with ; " malonimide " (128) and its substitution products are more common ; but it is doubtful if their nomenclature is ever referred to the systematic " 1, 3-epaminopropandione-1, 3 ". Derivatives of rings containing two nitrogen atoms are " aziethane " and " ethidene urea " compounds respectively, (129) and (130). They are of little general interest.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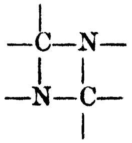
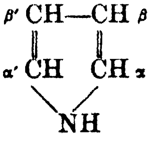
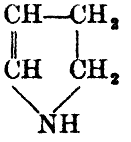

(130)

FIVE-MEMBERED NITROGENOUS RINGS

In this case the nucleus which gives rise to many of the trivial names of the series, is " pyrrole " (131), this molecule becoming successively hydrogenated to " pyrroline " (132) and " pyrrolidine " (133). The last two compounds are, more systematically, " dihydro- " and " tetrahydro-pyrrole " ; but the principle of alteration of terminals is accepted by the Liège convention (Rule 60). It may be added that certain of the carbonyl derivatives of the pyrrolidine ring are not usually named systematically. Thus, (134) " 1, 4-epaminobutanone-1 " is called " butyrolactam " ; while " succinimide " (135) is not termed " 1, 4-epaminobutandione-1, 4 ".



(131)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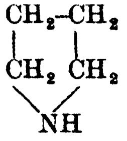
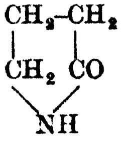

(133)

The substituted derivatives of pyrrole often have the positions of their substituent groups indicated according to the scheme of (131) ; thus (136) is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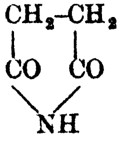
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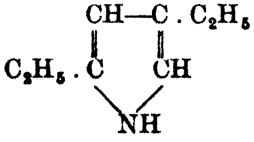
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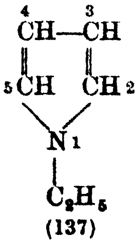
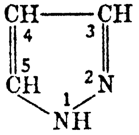


(137)

" α, β'-diethylpyrrole " ; (137) is " N-ethylpyrrole ". The numerical system of identification of substituent positions is also used, as in (137), but, although more systematic, is less frequently met with than the former system. Compounds obtained by inserting additional nitrogen atoms into the pyrrole ring, have a semi-systematic nomenclature, which is extended to most similar rings. Thus, all compounds containing two nitrogen and three carbon atoms in the ring are "pyrro-α-monazole" or "pyrro-β-monazole" derivatives; all those with three nitrogen and two carbon atoms are "pyrrodiazoles", of which there are four groups, αα′, αβ, αβ′, and ββ′. Three additional nitrogen hetero-atoms in pyrrole give "pyrrotriazoles". In actual practice, these names are seldom used; the two pyrro-monazoles are called "pyrazole" and "imidazole" or "glyoxaline" (138) and (139). The pyrazole ring is enumerated as in (138)



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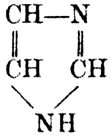

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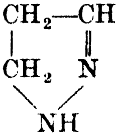
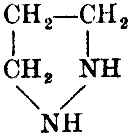
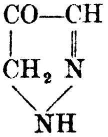


(140)

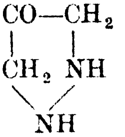


(141)

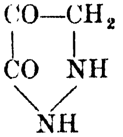
and formulæ (139-144) show a series of important compounds from this nucleus. "Pyrazoline" (140) and "pyrazolone" (142) are the dihydro- and keto-dihydro- derivatives respectively, while complete hydrogenation gives "pyrazolidine" (141), a substance readily converted into "pyrazolidone" (143) and "diketo-pyrazolidone" (144). The older systematic name for the latter



(142)



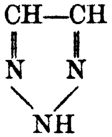
(143)



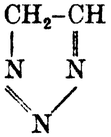
(144)

would be "tetrahydropyrro-2-monazole-dione-4, 5", although "1, 3-hydrazi-propandione-1, 2" is more succinct.

Nomenclature of rings containing three nitrogen and two carbon atoms is complicated by tautomerism. Thus, there are three 1, 2, 3-triazoles structurally possible (145-7):—



(145)



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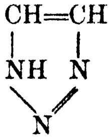
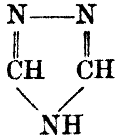


(147)

Derivatives of the first two are known, and using numerical indications for substitution, no ambiguity arises. The 1, 2, 4 triazoles (148-150) also exist in three tautomeric forms:—



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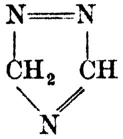

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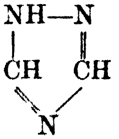
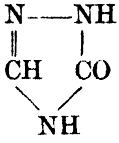
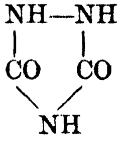


(150)

but enumeration from the single nitrogen atom removes any ambiguity in nomenclature. In each the formation of a dihydro-derivative is signified in the name by the alteration of the termination "-ole" to "oline"; the formation of a tetrahydro derivative by a change to "olidine"; a keto group is

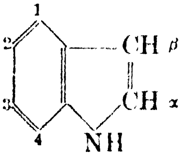

(151)


(152)

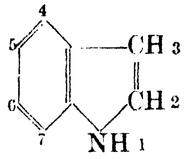
usually shown by the change of the final syllable to "one". Thus (151) is a triazolinone, and (152) is "diketo-triazolidine"; it is usually called "urazole".

CONDENSED PYRROLE NUCLEI

There is very little system about the naming of the condensed heterocyclic nuclei and trivial names are the rule rather than the exception. Thus, "benzpyrrole" (153) is nearly always called "indole", and is numbered as shown; the older system of referring to the substituted compounds of this nucleus was to term a compound with the substituent on the nitrogen an "N" derivative, and to differentiate the carbon atoms of the pyrrole ring as "α" and "β", the benzene carbon atoms being numbered as in (153). The fully numbered ring (154) is to be preferred. Trivial names for the derivatives of indole abound; "3-methyl indole" (155) is called "skatole"; "2-methyl indole" is "α-methol ketol" (156), etc. It may be pointed out that certain derivatives of the series must be referred to the skeleton (157), "indolenine", for naming. One has only to turn to the pages of a reference book such as Richter's *Organic Chemistry*, Part III, to observe the tenacity with which the trivial name system has been adhered to; strange names such as "imino-oxydiazoline", and "benzoazimidol" abound, but with the rapid growth of the subject, it is probable that the more systematic method will be more widely used, for all save the simplest rings.



(153)



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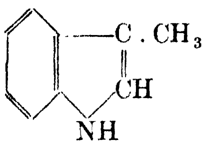

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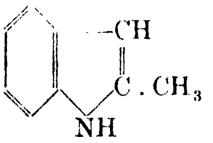

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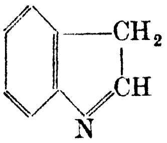
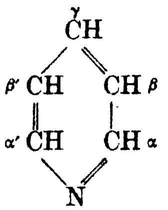


(157)

SIX-MEMBERED RINGS

The parent of this series is "pyridine" (158); the nuclei derived from it are named trivially, without reference to any system other than an analogy with the procedure used in the case of the five-membered rings already described. The general trend of such nomenclature is discussed in Chap. VII, Vol. II. The older system of enumeration of substituents in the pyridine ring is given in (158) side by side with the more modern and certainly more convenient system of enumeration from the pyridine nitrogen as "1". A similar alternative state of nomenclature characterises the compounds in which oxygen is present as a hetero-atom; it should be noted that the terms "furan" and "pyran"



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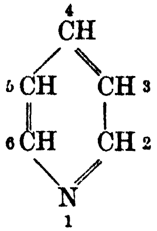
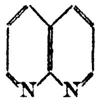
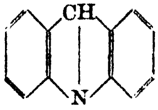
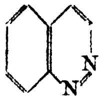
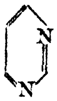
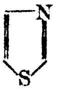
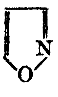
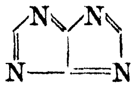


are used for unsaturated rings, a practice which avoids inconsistentcy with the "-ane" termination of saturated hydrocarbons (Rule 4, Liège convention). Rule 16 of the Liège system is seldom used except for new substances, although in some cases it could clarify nomenclature; according to this system the heterocyclic ring is referred to the corresponding hydrocarbon ring (usually aromatic) to obtain the stem name; thus "pyridine" becomes "azabenzene" "quinoline" and "isoquinoline" would be "1-azanaphthalene" and "2-azanaphthalene" respectively. Further examples are :—

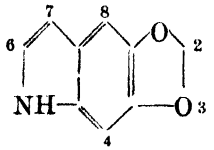
Structure	Accepted trivial name	Name according to Rule 16
	Napthyridin	1, 8-Diazanaphthalene
	Acridine	10-Azanthracene
	Cinnoline	1, 2-Diazanapthalene
	Pyrimidine	1, 3-Diazabenzene
	Thiazole	3-Azathiophen or 1, 3-Thiaza*cyclo*pentadiene
	Isoxazole	2-Azafuran

It would be advantageous to use the system for all but the simplest rings, and a list could be compiled of accepted trivial ring names.

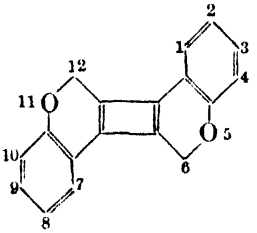
In many cases, the correct (or previously accepted) name of a complex ring is hard to find; the 1913-22 Collective Index to the Chemical Society's publications has an excellent collection of some 400 important types. In all cases of doubt and difficulty reference should be made to the *Ring Index* (A.C.S. Monograph No. 84), compiled under the editorship of A. M. Patterson and L. T. Capell. Published in 1940, this volume contains an indexed catalogue of over 4000 ring types. The following entries are chosen from this collection to illustrate the type of problem which may be encountered in ring nomenclature.[1]



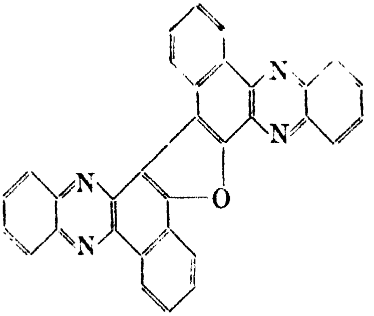
604. $C_4H_2N_4$. Imidaz[d]imidazole.



1385. $C_9H_7NO_2$. 5-[1, 3]Dioxolo[f]indole (5, 6-Methylenedioxyindole).

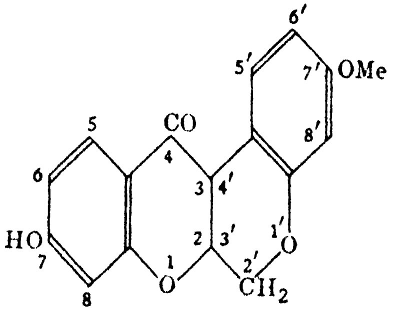


2882. $C_{18}H_{12}O_2$.
6, 12 *Cyclo*buta[1, 2-c, 3, 4-c′]-bis[1]benzpyran.



3291. $C_{32}H_{16}N_4O$.
Dibenzo[c, c′]furo[2, 3-a, 4, 5-a′] diphenazine.

In discussing ring nomenclature Clarence Smith gives the example :—



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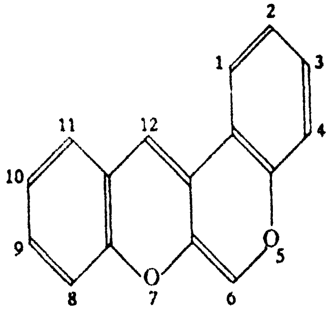

(160)

which, since it is a fusion of the chromone and chromene rings, may be referred to as " 7-hydroxy-7′-methoxychromeno-3′, 4′, 2, 3-chromone " (159). Here it is preferable to refer the name to the largest ring structures the names of which are universally accepted, a point which is obvious when the name already given is compared with the name according to the system proposed by the International Union of Chemistry, viz. " 6-hydroxy-9-keto-4′-methoxy-4, 9-dihydro-3, 10-dioxa-1, 2-benzanthracene ". On the other hand, the *Ring Index* (No. 2762) refers to the structure (160) which is differently enumerated; " [1] Benzopyrano [3, 4b] [1]-benzopyran " ; the 6, 12-dihydro derivative is, however, regarded by the compilers of the *Ring Index* as " chromeno (3′, 4′, 2, 3)chromane ".

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[1] The actual formulæ of the Ring Index contain no double-bonds ; these have been inserted to bring the cited examples into line with the remainder of the formulæ in this volume.

In this review of nomenclature numerous classes have been omitted, such, for example, as organic sulphur compounds, organo-metallic compounds, acid chlorides, anhydrides, amides, etc. Where necessary their nomenclature will be discussed with their chemistry in the appropriate chapter.

Rapid expansion of organic chemistry has led to discovery of an enormous number of compounds, many of which are purely synthetic and have no natural occurrence. In 1885, Odling, addressing the British Association, actually made a strong plea for the use of trivial names so that each substance had a convenient short name ; he deplored the coming of systematic names, thus :—

> " There seems, moreover, at the present time, and especially among the younger chemists, to be a growing preference for structural or so-called constitutional names."

Such preference has, by necessity, become universal, and it has been recognised that although a strict adherence to systematic nomenclature is not at all times convenient, owing to the length of the names so obtained, the systematic name is often the most lucid and easily understood.

The following remarks of Clarence Smith who, as Editor of the Chemical Society's publications for many years, has done much for chemical nomenclature, may be quoted in conclusion :—

> " . . . may I make a plea for the chemists of the future ? For them, the modern craze for brevity in names is storing up trouble. Fifty years hence, students will have to learn the names and empirical formulæ of, possibly, thousands of compounds, and we now could save them all that mental labour by using systematic names instead of empirical ones. Tetralin and dekalin are industrial names, but they have got into scientific literature because the names tetrahydro- and decahydronaphthalene involve the trouble of writing a few more letters. Recently, I had to deal with the name " thionessal ", coined more than fifty years ago. How many of you could, off-hand, give the scientific name and formula of this compound ? From what I have said to-night you might guess that it is an aldehyde containing the thione radical. You would be wrong. When the compound is named 2, 3, 4, 5-tetraphenylthiophene, you all know what it is and can write the formula."

APPENDIX I

RULES PROPOSED BY THE LIÈGE CONFERENCE (1930)

I. GENERAL.

1. **As little change as possible is to be made to existing nomenclature.**
2. **The system is concerned, at present, only with compounds whose constitution is known, leaving to some future date consideration of compounds the constitution of which is imperfectly known.**
3. **The words, suffixes, etc., of these rules must be adapted to the various languages by the appropriate sub-committees.**

II. HYDROCARBONS

4. The suffix "*-ane*" is adopted for saturated hydrocarbons; acyclic hydrocarbons are known generically as '*alkanes*'.
5. The existing names—"methane", "ethane", "propane", "butane"—of the first four hydrocarbons are preserved; for the remainder, names derived from the Greek or Latin numbers are to be used.
6. Branched-chain (arborescent) hydrocarbons are regarded as derivatives of normal hydrocarbons; their names are referred to the longest carbon chain which can be established in the molecule, adding the designations of the lateral chains. In cases of ambiguity, or if by doing so a more simple name can be attained, the fundamental chain is taken to be that with the maximum of substituents.[1]
7. Where several lateral chains exist, the order of their announcement is in increasing order of complexity. The chains carrying the largest number of secondary or tertiary atoms are considered the most complex. Where two or more different groups of equal complexity are involved alphabetical order should be followed.
8. In unsaturated acyclic hydrocarbons, with a single double bond, the suffix "-ane" is replaced by "-ene"; if two double bonds are present the ending "-diene" is used; and so on. The generic name for such hydrocarbons would be 'alkenes', 'alkadienes', 'alkatrienes', etc., e.g. "propene", "hexene".
9. Names of hydrocarbons containing triple bonds end in "-yne", "-diyne", etc. The generic name is 'alkyne', e.g. "propyne", "heptyne".
10. In the presence of both double and triple bonds the terminations "-enyne", "-dienyne", etc., are used. Generic names of such hydrocarbons would be 'alkenynes' or 'alkadienynes'.
11. Saturated monocyclic hydrocarbons take their name from the corresponding acyclic saturated hydrocarbon, preceded by the prefix "*cyclo*". They have the generic title '*cyclo*alkanes'.
12. When unsaturated (the cyclic hydrocarbons) the Rules 8-10 are applied. Also, in the case of aromatic, polycyclic compounds, partially saturated, the prefix "hydro" preceded by di, tetra, etc., is used. E.g. "dihydroanthracene".
13. Aromatic hydrocarbons are indicated by the suffix "-ene", and conserve generally their customary names. It is permitted to use the word "phene" in place of "benzene".

III. FUNDAMENTAL HETEROCYCLIC COMPOUNDS

14. Suffixes of customary names, which do not correspond with the functional group (implied) are altered according to the peculiarities of each language, e.g.:—
    (*a*) The suffix "-ol" is changed to "-ole" as in "Pyrrole".
    (*b*) The suffix "-ane" is changed to "-an" as in "Pyran".

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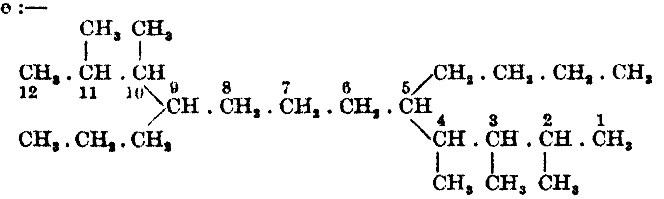
[1] Example :—

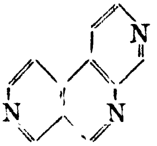


In this example there are four ways in which the dodecane chain may be selected; if chosen as marked the substance is named "2, 3, 4, 10, 11-pentamethyl-9-propyl-5, butyl-dodecane"; had the stem been chosen in any of the alternative ways a much more cumbrous name would have resulted.

15. When nitrogenous heterocyclic compounds (not having the termination " ine ") are hydrogenated progressively to basic compounds this derivation is marked by successive changes of the termination to " ine " and " idine ". E.g. :—

" Pyrrole ", " pyrroline ", " pyrrolidine " ;
" oxazole ", " oxazoline ".

16. The final letter " a " is adopted for hetero atoms which form part of a ring. Thus, oxygen is indicated by " oxa " ; sulphur by " thia " ; nitrogen by " aza ", etc. It may, perhaps, be necessary to suppress the " a " before a vowel. Examples : " thiadiazole ", " oxadiazole ", " thiazine ", " oxazine ", whilst preserving those names of heterocyclic compounds which have been universally adopted, the names of other heterocyclic compounds are derived from the corresponding homocyclic compounds, e.g. (161) is " 2, 7, 9-triazaphenanthrene ".



(161)

IV. Simple Functions

17. Compounds of simple function are those which comprise a function of one type only, although the functional group may be repeated several times in the same molecule.
18. When only a single functional group is present, the stem shall be chosen so as to contain it ; where there are several functional groups the stem is so determined that it contains the maximum number of functional groups.
19. Halogen compounds are designated by the name of the hydrocarbon from which they are derived, preceded by a prefix indicating the nature and number of the halogen atoms.
20. Alcohols and phenols take the name of the hydrocarbon from which they are derived, followed by the suffix " -ol ". In accord with Rule 1 the names such as " phenol ", " cresol " and " naphthol ", which have been universally adopted, are preserved. The same nomenclature may be extended to heterocyclic compounds, e.g. " quinolinol ".
21. In dealing with polyhydroxy alcohols or phenols one of the particles di-, tri- and tetra- is intercalated between the name of the hydrocarbon stem and the suffix " -ol ".
22. The name " mercaptan " is abandoned as a suffix ; the function is indicated by the suffix " thiol ".
23. Ethers—or oxides, are considered as hydrocarbons in which one or more hydrogen atoms have been replaced by alkoxy groups. At the same time, for symmetrical ethers (oxides), the accepted nomenclature is preserved. E.g. $CH_3O \,.\, C_2H_5$ " methoxyethane " ; CH_3OCH_3, " methoxymethane " or " methyl ether ".
24. Oxygen linking two atoms of a carbon chain is designated by the prefix " epoxy ", in all cases where it is inexpedient to name the substance as a cyclic compound.[1] Examples : " ethylene oxide " = " epoxyethane "

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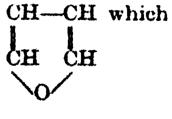
[1] This proviso is to except from the rule such substances as furan which would otherwise be called " 1, 4 epoxybutadiene-1, 3 ".



"epichlorhydrin" = "1, 2-epoxy-3, chloropropane"; "tetramethylene oxide" = "1, 4-epoxybutane".

25. Sulphides, disulphides, sulphoxides and sulphones are named as the ethers (oxides), 'oxy' being replaced by 'thio', 'dithio', 'sulphinyl' or 'sulphonyl'. Examples: $CH_3 . SO_2 . C_2H_5$ = "methylsulphonylethane"; $CH_3 . S . C_3H_7$ = "methylthiopropane";
$CH_3(CH_2)_2SO(CH_2)_3CH_3$ = "(propylsulphinyl)-1-butane".
26. Aldehydes are characterised by the suffix "-al" added to the name of the hydrocarbon from which they are derived; thioaldehydes take the suffix "-thial"; acetals are named as "1, 1-dialkoxyalkanes".
27. Ketones are accorded the distinguishing suffix "-one"; diketones, triketones and thioketones are designated by the suffixes "-dione", "-trione", "-thione".
28. The name "ketone" is retained.
29. For acids, the Geneva nomenclature is retained. However, in cases where its application is tedious, the carboxyl group may be considered as a substituent and the name of the acid formed by adding the suffix "-carbon" or "-carboxylic" (according to the language) to the name of the hydrocarbon stem.
30. Acids in which an atom of sulphur has replaced an atom of oxygen, are named according to Geneva nomenclature. Examples: "ethanethioic", "ethanethiolic", "ethanethionic", "ethanethionthiolic".[1] Or, considering the carboxyl group as a substituent; one would designate them "carbothioic" acids, employing the term
"carbothiolic" if the oxygen of the —OH is replaced by sulphur;
"carbothionic" if the oxygen of the =CO is replaced by sulphur; and
"carbodithioic" if both oxygen atoms are replaced.
31. The existing nomenclature for salts and esters is retained.
32. Acid anhydrides retain their present method of nomenclature, after the names of their corresponding acids. In accordance with the Geneva system, the amides, amidoximes, amidines, imides and nitriles are denoted by adding these terminations to the name of the hydrocarbon stem, whilst the acid halogenides are named by combining the term "halide" with the name of the radicle. Examples: $C_3H_7 . COCl$, "butanoyl chloride"; $C_3H_7 . CO . NH_2$, "butanamide". If the carboxyl group is considered as a substituent the terminations "carbonamide", "carbonamidine", "carbonamidoxime", "carbonimide", "carbonitrile" are employed. Examples: C_3H_7COCl, "propanecarbonyl chloride"; $C_3H_7CONH_2$, "propanecarbonamide", etc.
33. The ending "-ine" is reserved exclusively for the nitrogenous bases. The existing nomenclature of monamines is retained. For polyamines the name of the hydrocarbon stem is followed by the suffixes "-di", "-triamine", etc. With aliphatic bases containing pentavalent nitrogen, the termination "-ine" is changed to "-onium". Of cyclic substances containing pentavalent nitrogen as part of the ring, those ending in "-ine" are changed to "-inium", those ending in "-ole" to "-olium". Examples: "pyridine", "pyridinium"; "imidazole", "imidazolium.
34. Nomenclature of derivatives of phosphorus, arsenic, antimony and bismuth is very complex, and will be considered later.

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[1] As Grignard points out (p. 1088, Vol. I, *Traité de chimie organique*), this nomenclature is faulty,

if "thioic" = —CS . SH
„ "thiolic" = —CO . SH
„ "thionic" = —CS . OH

the term "thionthiolic" is redundant and likely to cause confusion.

35. Compounds derived from hydroxylamine by replacement of the hydrogen of the hydroxyl are to be considered as alkoxyl derivatives; those in which a hydrogen atom of the —NH_2 group has been replaced, as alkylhydroxylamines. Oximes are named by adding the suffix "-oxime" to the name of the aldehyde, ketone or quinone from which they are derived. Examples: $C_2H_5ONH_2$, "ethoxyamine"; C_2H_5NHOH, "ethylhydroxylamine".
36. The generic term "urea" is retained; it may be used as a suffix to indicate the alkyl and acyl derivatives of urea. Examples:—

    $C_4H_9NH . CONH_2$, "butyl urea"; $C_3H_7 . CO . NH . CO . NH_2$, "butyryl urea".

    The bivalent radicle —NH . CO . NH— is to be called "urylene".
37. The generic term "guanidine" is retained.
38. The generic term "carbylamine" is retained.
39. Isocyanic and isothiocyanic esters (RNCO, RNCS) are referred to as "isocyanates" and "isothiocyanates".
40. The name "cyanate" is reserved for the true esters of cyanic acid, which furnish the latter or its hydrolysis products on saponification. The term "sulphocyanate" is replaced by "thiocyanate".
41. Nitro derivatives; no change in the normal current method of nomenclature.
42. The denominations "azo" and "azoxy" are retained.
43. (*a*) Diazonium compounds $R . N_2X$ are named by the addition of the word "diazonium" to the name of the parent substance (e.g. "benzene diazonium chloride").

    (*b*) Compounds possessing the same generic formula, but with trivalent nitrogen are named by replacing the "diazonium" of the previous section, by "diazo" (e.g. "benzene diazo hydroxide").

    (*c*) Substances of the type RN_2OMe are designated "diazotates".

    (*d*) Compounds in which two atoms of nitrogen are attached to a single carbon atom are distinguished by the prefix "diazo". Examples:— "diazomethane", "diazoacetic acid".

    (*e*) The denomination "diazoamino" is retained; although one can consider these bodies as derivatives of "triazene".

    (*f*) Derivatives of the substances

    $H_2N . NH . NH . NH_2$, $NH{=}N . NH . NH_2$, $NH{=}N . NH . N{=}NH$

    are named "tetrazanes", "tetrazenes", "pentazdienes".
44. Hydrazines are designated by the name of the radicles from which they are derived followed by the suffix "-hydrazine". In the case where the amino group of a carbonamide is replaced by the hydrazino group, the suffix "-hydrazide" is employed. The hydrazoic derivatives are considered as derivatives of hydrazine. Examples:—$CH_3 . NH . NH_2$, "methylhydrazine"; $C_2H_5 . NH . NH . C_3H_7$ "1-ethyl-2-propyl hydrazine"; $C_3H_7 . CO . NH . NH_2$; "butyrhydrazide" or "propane carbohydrazide".
45. Hydrazones and semicarbazones are named in a manner similar to that of the oximes; the denomination "osazones" is retained.
46. The name "quinone" is retained.
47. The sulphonic and sulphinic acids are designated by the addition of the suffixes "-sulphonic" or "-sulphinic" to the name of the hydrocarbon. The analogous acids of selenium and tellurium have the names "alkaneselenonic" and "seleninic"; "alkane telluronic" and "tellurinic".
48. Organometallic compounds are designated by the names of the organic radicles attached to the metal, followed by the name of the latter.

Examples : " dimethylzinc ", " tetramethyllead ", " methyl magnesium chloride ". In the case of a metal tied to a complex radicle it is permissible to consider it as a substituent, e.g. $ClHg . C_6H_4 . COOH$, " chloromercuribenzoic acid ".

49. The nomenclature of cyclic derivatives with lateral chains will be considered later.
50. Where it becomes necessary, to avoid ambiguity, the names of radicles can be placed in parentheses, e.g. " (Dimethylphenyl)amine " = $(CH_3)_2C_6H_3 . NH_2$; " phenyldimethylamine " = $C_6H_5 . N(CH_3)_2$.

V. COMPLEX FUNCTIONS

51. Compounds of complex function, i.e. compounds in which diverse functions are present, only one function (the principal function) can be indicated by the termination of the name. The other functions are designated by suitable prefixes.[1]
52. In the designation of functions, the following prefixes and suffixes are employed :—

FUNCTION	PREFIX	SUFFIX
Acids and acid derivatives	Carboxy	Carboxylic, carbonyl, carbonamide, etc., or -oic, -oyl, etc.
Alcoholic	Hydroxy	Ol
Aldehyde	Oxo, aldo (for O ; aldehydo or formyl for CHO)	Al
Amine	Amino	Amine
Pentavalent nitrogen	—	-onium, -inium
Nitrile	Cyano	Nitrile
Ketone	Oxo or keto	-one
Azo derivative	Azo	—
Azoxy ,,	Azoxy	—
Nitro ,,	Nitro	—
Nitroso ,,	Nitroso	—
Sulphinic ,,	Sulphino	Sulphinic
Sulphonic ,,	Sulpho	Sulphonic
Ether (oxide)	Alkoxy	—
Halogen compound	Halogeno	—
Hydrazine	Hydrazino	Hydrazine
Double link	—	-ene
Triple ,,	—	-yne
Mercaptan	Mercapto	Thiol
Oxide, (Ethylene, etc.)	Epoxy	—
Sulphone	Sulphonyl	—
Sulphoxide	Sulphinyl	—
Sulphide	Alkoylthio	—
Urea	Ureido	Urea

53. Names of compounds derived from the fundamental heterocyclic rings are formed according to the preceding rules.

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[1] Rules 51-2 are particularly unsatisfactory ; the Commission refused to define, or admit the need for definition of, the term ' principal function ', thus $HOOC . (CH_2)_3 . CHO$ (described in Chap. II as " pentanal-1, acid-5 ") would be described according to rules 51-2 either as " 4-carboxybutanal-1 ", or " 5-aldopentane, acid-1 ".

VI. RADICLES

54. Univalent radicles derived from saturated aliphatic hydrocarbons by loss of an atom of hydrogen, are named by replacing the termination " -ane " by " -yl ".
55. Names of univalent radicles, derived from unsaturated aliphatic hydrocarbons, are distinguished by the termination " -enyl ", " -ynyl ", " -dienyl ", the positions of the double or triple bonds being indicated by figures where necessary.
56. Bivalent or trivalent radicles derived from saturated hydrocarbons by the loss of 2 or 3 atoms of hydrogen from the same atom of carbon are denominated by replacing the " -ane " termination of the hydrocarbon by the termination " -ylidene " or " -ylidine ". For radicles derived from unsaturated hydrocarbons, the terminations are adjusted to the name of the hydrocarbon. The terms " isopropylidene " and " methylene " are retained.
57. Bivalent radicles, derived from aliphatic hydrocarbons by the loss of an atom of hydrogen from each of two terminal carbon atoms, are named " ethylene ", " trimethylene ", " tetramethylene ", etc.
58. Radicles derived from acids by removal of the —OH, are described by transforming the " carbonic " or " carboxylic " to " carbonyl " or " oyl ", using the Geneva system.
59. Univalent radicles derived from aromatic hydrocarbons by removal of one atom of hydrogen from the nucleus are, in principle, named by altering the termination " -ene " to " -yl ". The radicles C_6H_5— and $C_6H_5 . CH_2$— still continue to be called " phenyl " and " benzyl ". In addition, certain abbreviations sanctioned by custom are authorised, such as " naphthyl " in place of " naphthalyl ".
60. Univalent radicles derived from heterocyclic compounds by removal of hydrogen from the nucleus, are named by turning the terminal " -ine " to " -yl ". In cases where ambiguity arises the final " e " only is changed to " -yl ". Examples : " pyridine ", " pyridyl " ; " indole ", " indolyl " ; " pyrroline ", " pyrrolinyl " ; " triazole ", " triazolyl " ; " triazin ", " triazinyl ".
61. Radicles, formed by the removal of an atom of hydrogen from the lateral chain of a cyclic compound, are considered as substituted aliphatic radicles.
62. In general, special names are not given to polyvalent radicles derived from cyclic compounds by loss of more than one atom from the nucleus. In such cases, prefixes or suffixes are used. Examples : " triaminobenzene " or " benzene triamine " ; " dihydroxypyrrole " or " pyrrolediol ".
63. The order of enunciation of radicles or prefixes (order alphabetic or conventional) is a matter of choice.

VII. ENUMERATION

64. In aliphatic compounds, the carbon atoms of the stem are numbered from one end to the other, employing arabic numerals ; in cases where ambiguity is likely to arise the lowest numbers are given (1) to the ' principal function ', (2) to double bonds, (3) to triple bonds, (4) to atoms or radicles designated by the prefixes ; the term ' lowest number ' signifies that group containing the smallest numerals. Thus, 1, 3, 5 is less than 2, 4, 6 ; 1, 5, 5 less than 2, 6, 6 ; 1, 2, 5 less than 1, 4, 5 ; 1, 1, 3, 4 less than 1, 2, 2, 4.
65. Positions in a lateral chain are designated, from the point of attachment, by numerals or letters. Such numerals or letters are, with the name of the chain, placed in parentheses.

66. In case of ambiguity in the enumeration of atoms or radicles designated by prefixes, the order is chosen so that the prefixes are immediately before the name of the stem, or of the lateral chain in which they are substituents.

67. Prefixes " di- ", " tri- ", " tetra- ", etc., are used in simple expressions (e.g. " diethylbutanetriol ") and the prefixes, " bis- ", " tris- ", " tetrakis- ", etc., in more complicated instances.
Examples :
" bis(methylamino)propane ", $CH_3 . NH(CH_2)_3NH . CH_3$
" bis(dimethylamino)ethane ", $(CH_3)_2N . CH_2 . CH_2 . N(CH_3)_2$.
The prefix " bi- " should never be used, save to indicate the doubling up of a radicle or compound, for example " biphenyl ".

68. A catalogue of the cyclic structures and their enumeration according to present usage, and to the system of Patterson, is in preparation under the ægis of the National Research Council of the United States and of the American Chemical Society. Finally, to avoid confusion, the Commission recommends that the system of enumeration be included in each memoir.

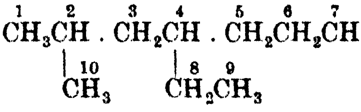
APPENDIX II

A NEW NOTATION FOR ORGANIC COMPOUNDS

The extreme difficulties of systematic nomenclature based on the older systems will have become apparent to those who have read the main portion of this Chapter, whilst a glance at the examples set out in the Ring Index will confirm this view.

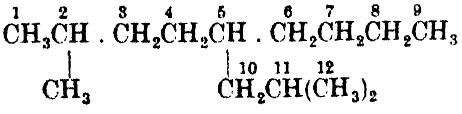
In an attempt to avoid the various pitfalls of the older nomenclatures Dyson has evolved a new mode of delineating organic structures.[1] According to this system all compounds are divided into two classes ; those in which the (ignoring heterocyclic atoms) carbon atoms are all joined together (homogeneous) and those in which the various portions of the carbon skeleton are separated by functional groups (as the two ethyl groups in ordinary ether) (heterogeneous). A homogeneous structure is derived from a single hydrocarbon ; a heterogeneous structure is derived from several indirectly linked hydrocarbons.

The aim of the new notation is to reduce the structural ideograph to a linear form which shall be completely unambiguous both as to statement and enumeration. In order to attain this end, the hydrocarbon structure is considered first. Thus, a homogeneous hydrocarbon structure may consist of a chain (straight or arborescent), a ring, an aggregate of rings or an admixture of chains and rings. All acyclic hydrocarbons are delineated by selecting the longest carbon chain present and indicating its presence by a statement such as " C_{10} " or " C_{13} " (decane and tridecane respectively). If there are no branch chains this statement suffices ; in arborescent structures the statement of the longest chain is followed by the statement of the subsidiary chains in decreasing order of size. Thus the examples of saturated acyclic hydrocarbons given in the body of the Chapter (examples 1-3) would be delineated thus :—



$$\overset{1}{\mathrm{C}}\mathrm{H_3}\underset{\overset{10}{\mathrm{CH_3}}}{\overset{2}{\mathrm{C}}\mathrm{H}}\;.\;\overset{3}{\mathrm{C}}\mathrm{H_2}\underset{\overset{8\;\;9}{\mathrm{CH_2CH_3}}}{\overset{4}{\mathrm{C}}\mathrm{H}}\;.\;\overset{5}{\mathrm{C}}\mathrm{H_2}\overset{6}{\mathrm{C}}\mathrm{H_2}\overset{7}{\mathrm{C}}\mathrm{H_3}$$

$C_7 . C_2, 4 . C, 2$



$$\overset{1}{\mathrm{C}}\mathrm{H_3}\underset{\mathrm{CH_3}}{\overset{2}{\mathrm{C}}\mathrm{H}}\;.\;\overset{3}{\mathrm{C}}\mathrm{H_2}\overset{4}{\mathrm{C}}\mathrm{H_2}\underset{\overset{10\;\;11\;\;12}{\mathrm{CH_2CH(CH_3)_2}}}{\overset{5}{\mathrm{C}}\mathrm{H}}\;.\;\overset{6}{\mathrm{C}}\mathrm{H_2}\overset{7}{\mathrm{C}}\mathrm{H_2}\overset{8}{\mathrm{C}}\mathrm{H_2}\overset{9}{\mathrm{C}}\mathrm{H_3}$$

$C_9 . C_3, 5 . C, 2, 11$

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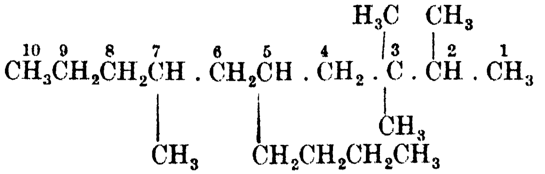
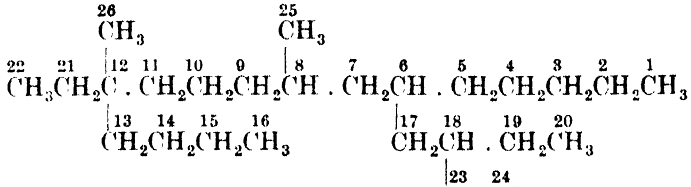
[1] See Appendix III.



$CH_3CH_2CH_2CH(CH_3) . CH_2CH(CH_2CH_2CH_2CH_3) . CH_2 . C(CH_3)_2 . CH(CH_3) . CH_3$

$C_{10} . C_4, 5 . C, 2, 3, 3, 7$



$CH_3CH_2C(CH_3)(CH_2CH_2CH_2CH_3) . CH_2CH_2CH_2CH(CH_3) . CH_2CH(CH_2CH(CH_2CH_3) . CH_2CH_3) . CH_2CH_2CH_2CH_2CH_3$

$C_{16} . C_4, 6 . C_2, 12, 18 . C, 8, 12$

The saving of space is manifest ; the sequential enumeration of the carbon atoms avoids any difficulties in numbering substituent groups, and the final results can be listed in index form.

The presence of unsaturation in such hydrocarbons is indicated by modulated forms of E :—

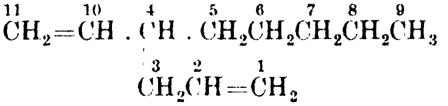
E Double bond.
E3 Triple bond.

E1 and E2 may be used to delineate the *cis*- and *trans*-arrangement of groups at the double bond respectively.

Several examples (4-12) from the main part of this Chapter are used below to illustrate this principle :—

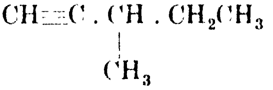
$\overset{1}{C}H_3\overset{2}{C}H_2\overset{3}{C}H{=}\overset{4}{C}H . \overset{5}{C}H_2\overset{6}{C}H_3$ $C_6 . E, 3$

$\overset{1}{C}H_3\overset{2}{C}H_2\overset{3}{C}H{=}\overset{4}{C}H . \overset{5}{C}H{=}\overset{6}{C}H . \overset{7}{C}H_2\overset{8}{C}H_3$ $C_8 . E, 3, 5$



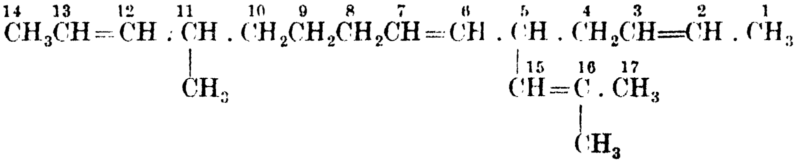
$CH_2{=}CH . CH(CH_2CH{=}CH_2) . CH_2CH_2CH_2CH_2CH_3$

$C_9 . C_2, 4 . E, 1, 10$



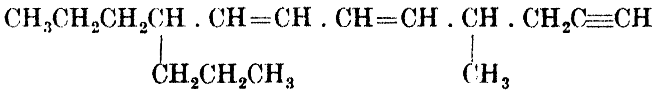
$CH{\equiv}C . CH(CH_3) . CH_2CH_3$

$C_5 . C, 3 . E3$



$CH_3CH{=}CH . CH(CH_3) . CH_2CH_2CH_2CH{=}CH . CH(CH{=}C(CH_3) . CH_3) . CH_2CH{=}CH . CH_3$

$C_{14} . C_3, 5 . C, 11, 16 . E, 2, 6, 12, 15$



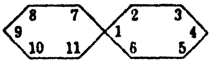
$CH_3CH_2CH_2CH(CH_2CH_2CH_3) . CH{=}CH . CH{=}CH . CH(CH_3) . CH_2C{\equiv}CH$

$C_{12} . C_3, 4 . C, 9 . E, 5, 7 . E3, 11.$

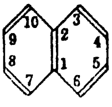
It will be noted from these examples that the unsaturation is cited after the chain is established, and that the longest carbon chain is always selected for the generating operation (in contradistinction to the Geneva-Liège system).

Single rings are delineated from the symbol A for fully saturated rings, and B for aromatic rings. The appropriate symbol is followed by a figure or series of figures indicating the nature of the individual units of the network.

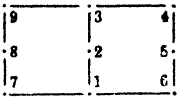
Thus, the simple *cyclo*paraffins are A3, A4, A5, A6, etc., whilst the fully unsaturated or aromatic types are B4, B5, B6, B7, etc. Fused rings are cited in terms of the units of the network ; thus, naphthalene is $B6_2$ and phenanthrene and anthracene are $B6_3$. To distinguish between the various types in each group the interfaces of the network units are enumerated. The comma separates the citation of the units from their enumeration. This principle is illustrated by the examples :—



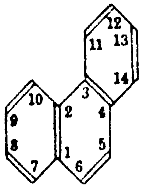
$A6_2$, 1-1



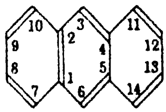
$B6_2$, 1-2[1]



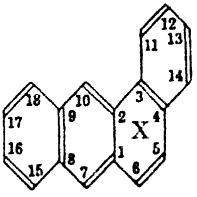
$A6_2$, 1-3



$B6_3$, 1, 3



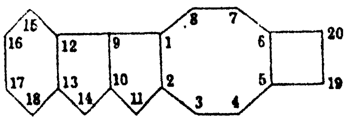
$B6_3$, 1, 4



$B6_4$, 1, 3, 8

The enumeration pattern is always chosen so that the first affected locant is as low as possible. Thus, in the example given as $B6_4$, 1, 3, 8, it is clear that any one of the three hexagon-hexagon interfaces could be numbered ' 1 '. To ensure that the next locant is ' 3 ' and not ' 4 ', enumeration must commence in the ring marked X ; even so, it could be commenced in two ways, and the indicated method is chosen so that the third locant shall be ' 8 ', and not ' 12 '. Note that once the proper ring has been selected for commencement of numbering, all subsequent numbers are added according to the order in which the locants were written down. In the example $B6_4$, 1, 3, 8 once the ring X has been properly enumerated, the numbering proceeds round the next ring from ' 1 ' to ' 2 ', followed by ' 3 ' to ' 4 ' and from ' 8 ' to ' 9 '.

If several different sized rings have been fused together as in



$A865_24$, 12, 1, 9, 5

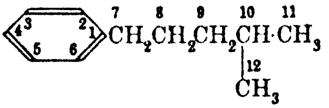
they are cited in order of decreasing size. The first ring cited is numbered first, and the subsequent locants indicate the position of attachment of the subsequent units of the network ; thus, the ' 12 ' in the citation above indicated the position of attachment of the six-ring. In this way ring systems can be unambiguously reduced to linear groups of symbols. The three examples mentioned and depicted in the body of the chapter as causing considerable difficulties of nomenclature are easily enough delineated :—

---

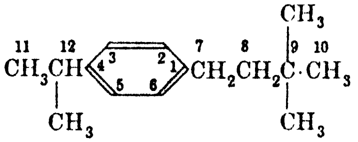
[1] The ' 1·2 ' is always abbreviated to ' 1 ' ; and where by so doing a ' 1 ' would appear solus, it is omitted. Thus $B6_2$ is always used for naphthalene and B65.H7, for indene.

Formula (21) $A65_2$, 1, 3-9.
Formula (22) $A6_35$, 1, 3, 7 . C_7, 17-19 . C, 3, 8, 22, 23 . E, 1-6, 4, 20 . Q, 13.
Formula (23) $A6_3$, 1, 1.

If a ring (or fused ring system) is joined to a chain, or to several chains, the ring is cited first and determines the whole enumeration of the aggregate, as in

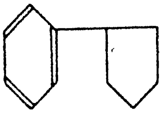


B_6 . C_5 . C, 10

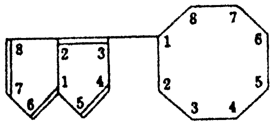


B_6 . C_4 . C_3, 4-12 . C, 9, 9

If two dissimilar rings are singly linked, the larger takes precedence (but all fused rings are senior to any single ring) as in :—

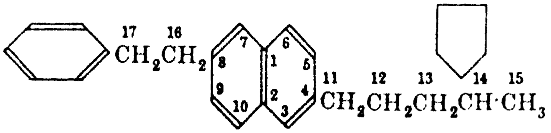


B6 . [A5]



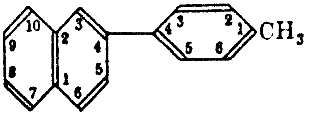
$B5_2$. [A8], 3

If the linkage of such rings takes place through a chain, the latter is considered to be an appendage of the senior group :—



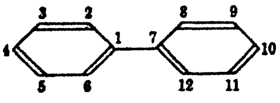
$B6_2$. C_5, 4 . C_2, 8 . [A5], 14 . [B6], 17

The use of square brackets, as shown in these examples, implies that the portion cited within the bracket is numbered independently, as though the link with the remainder of the molecule was non-existent. Where necessary the point of attachment to the bracketed moiety is shown just within the closing bracket, as in

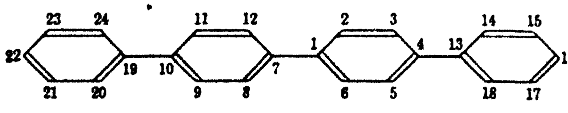


$B6_2$. [B6 . C . 4], 4

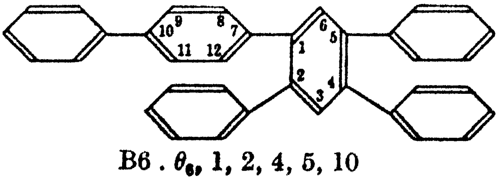
Strings or clusters of similar groups are delineated by the use of θ, which is used as a multiplying symbol. Thus :—



B6 . θ_2

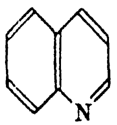


B6 . θ_4, 1, 4, 10

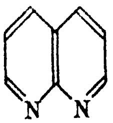


B6 . θ_6, 1, 2, 4, 5, 10

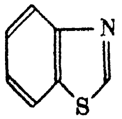
By the use, and extension, of these rules any hydrocarbon structure can be delineated and enumerated unequivocally. The heterocyclic bodies are delineated by reference to the parent homocyclic hydrocarbon using ZQ, ZS, ZN, ZP, etc., for hetero-oxygen, sulphur, nitrogen, etc. Some examples are :—



$B6_2$. ZN, 3



$B6_2$. ZN, 3, 10



B65 . ZS, 7 . ZN, 9 . H, 7

Functional groups are mainly dealt with as simple substituents by using the symbols :—

X	Carboxylic acid.
Q	Alcohol or phenol.
EQ1	Aldehyde.
EQ	Ketone.
S	Thiol.
ES	Thione, etc., etc.

Full details of the use of such symbols and the proper order for their citation will be found in the literature (see Appendix III). It is only possible here to give one or two instances of their application, e.g. :—

Formula No.	*Cipher.*
71	C_7 . C, 4 . X.
73	C_5 . C, 3 . X, 1, 5, 6.
76	A6 . [X . C_6 . C, 3 . 7].
89	$B6_3$, 1, 4 . C, 8 . H, 3, 6 . EQ, 3, 6 . N[A6 . Br . 4][C_6 . C, 3 . E, 3 . 6], 8.
91	$B6_3$, 1, 3 . N, 8.

APPENDIX III

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The introduction to Richter's *Lexicon der Kohlenstoffverbindungen*.

The introduction to Richter's *Organic Chemistry*.

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An excellent account of the methods used in U.S.A. for naming and indexing organic compounds is given in the introduction to the Subject Index of *Chemical Abstracts* for 1945.

G. M. Dyson, " A new notation and enumeration system for organic compounds ", 2nd Edn., 1949, London. (Longmans.)

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A. M. Patterson, *Rec. Trav. Chim.*, **48,** 1012 (1929).
A. M. Patterson, *J.A.C.S.*, **47,** 543 (1925).
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Some interesting historical references are :—

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" Nomenclature " (Appendix to Report of Anniversary Meeting, 1882), *J.C.S., 1882.*

" On some points in chemical nomenclature "—A. V. Harcourt, *Proc. Ashmolean Society* (New Series, No. 1).

" On chemical nomenclature "—G. C. Foster, *Phil. Mag.*, 1865.

CHAPTER III

THE HYDROCARBONS

> "Variety's the very spice of life."
>
> —COWPER.

The scope of organic chemistry is primarily due to the ability of one carbon atom to enter into valence arrangements with others producing almost all conceivable chains or patterns which, when combined with hydrogen, constitute the family of hydrocarbons; as mentioned in a previous chapter, the derivatives of these simple compounds obtained by the introduction of functional groups, comprise the vast range of organic compounds. In 1883, when Beilstein had published the first edition of his "Handbüch," Richter estimated the number of known organic compounds at 18,000; by 1910 the number was 150,000, and to-day it cannot fall far short of half a million. This half million is, of course, only a tithe of what could be produced should the necessity arise. Of the known organic compounds, about 4 per cent. are hydrocarbons. The upper limit of complexity in hydrocarbon formation is unknown; paraffin hydrocarbons with over seventy carbon atoms have been prepared, but there is no reason to suppose that the limit has been reached.

The hydrocarbons are divided into three main classes:—

(1) Acyclic.
(2) Alicyclic.
(3) Aromatic.

Acyclic hydrocarbons are either of straight or branched chain formation; alicyclic hydrocarbons contain a ring. Either class may be subdivided further into paraffin (or saturated) hydrocarbons, ethylenic or acetylenic types according to the degree of unsaturation present, and hybrid types containing any or all of these features can be produced. The aromatic hydrocarbons occupy a special category owing to the peculiar stability of the benzenoid structure, its remarkable reactivity and its ubiquity in natural substances.

The fully saturated acyclic hydrocarbons are termed 'paraffins', the name being derived from an early observation that the mineral waxes—the first substances to receive the name—are unreactive. The recognition of these waxes as higher members of the homologous series, led to the adoption of the name for the whole series. The unreactive nature of the higher members is modified in the lower paraffins which are capable of undergoing numerous reactions.

The natural occurrence of paraffin hydrocarbons in petroleum is dealt with in an Appendix to this chapter, but it must not be supposed that they are present in petroleum alone or that single pure substances can readily be obtained from the complex mixture. In petroleum, the saturated acyclic hydrocarbons are found mixed with a medley of alicyclic (naphthene) and aromatic hydrocarbons. In many cases, the branched chain forms occur in petroleum almost to the exclusion of the straight chain isomers, although under carefully controlled conditions of 'cracking' and 'reforming', predetermined mixtures of almost any isomers can be obtained.

Research in the higher realms of paraffin chemistry is complicated by numerous factors. In the first place, ultimate analysis is of little use for determining empirical formulæ in hydrocarbons above C_{17}, as may be seen from the table below, in which the differences between the carbon and hydrogen percentages of successive higher hydrocarbons is smaller than the probable accuracy of the analytical determination. Again, as will be observed from the table of the physical properties of normal paraffins below, the difference in the physical properties of successive members becomes so small in the higher regions of the series, that differentiation on these grounds is impossible, more especially as with the very high members of the series the melting points tend to be spread over several degrees. The third complicating factor is that of isomerism. These difficulties are well illustrated in the case of myricyl alcohol, the palmitic ester of which was stated to be the principal ingredient of beeswax; myricyl alcohol was, until recently, thought to be the alcohol $C_{30}H_{61}OH$, but

TABLE I

Hydrocarbon	Per cent. H	Per cent. C	Hydrocarbon	Per cent. H	Per cent. C
CH_4	25	75	$C_{17}H_{36}$	15	85
C_2H_6	20	80	$C_{22}H_{46}$	14·84	85·16
C_3H_8	18·18	81·82	$C_{24}H_{50}$	14·64	85·36
C_4H_{10}	17·24	82·76	$C_{60}H_{122}$	14·48	85·52
C_6H_{14}	16·28	83·72	Limiting value for		
$C_{16}H_{34}$	15·4	84·6	C_nH_{2n+2}	14·29	85·71

TABLE II

Hydrocarbon	Formula	B.P.	B.P. Increment	M.P.	M.P. Increment	
Methane	CH_4	— 164	—	— 184		
Ethane	C_2H_6	— 93	71	— 171·4		
Propane	C_3H_8	— 45	48	— 190		
Butane	C_4H_{10}	+ 0·6	45·6	— 135		
Pentane	C_5H_{12}	36	35·4	— 130·8		
Hexane	C_6H_{14}	69	33	— 93·7		
Heptane	C_7H_{16}	98·3	29·3	— 90		
Octane	C_8H_{18}	125·8	27·5	— 57		
Nonane	C_9H_{20}	149·5	23·7	— 51		
Decane	$C_{10}H_{22}$	173	23·5	— 32	19	
Undecane	$C_{11}H_{24}$	195	22	— 26·5		5·5
Dodecane	$C_{12}H_{26}$	215	20	— 12	14·5	
Tridecane	$C_{13}H_{28}$	234	19	— 6·2		5·8
Tetradecane	$C_{14}H_{30}$	252	18	5	11·2	
Pentadecane	$C_{15}H_{32}$	270	18	10		5·0
Hexadecane	$C_{16}H_{34}$	287	17	18	8·0	
Heptadecane	$C_{17}H_{36}$	303	16	22·5		4·5
Octadecane	$C_{18}H_{38}$	317	14	28	5·5	
Nonadecane	$C_{19}H_{40}$	330	13	32		4·0
Eicosane	$C_{20}H_{42}$	208/15 mm.	—	37	5·0	
Heneicosane	$C_{21}H_{44}$	219/15 mm.	—	40·4		3·4
Docosane	$C_{22}H_{46}$	230/15 mm.	—	44·4	4·0	
Tricosane	$C_{23}H_{48}$	240/15 mm.	—	47·7		3·3
Tetracosane	$C_{24}H_{50}$	250/15 mm.	—	51·1	3·4	
Pentacosane	$C_{25}H_{52}$	259/15 mm.	—	54		2·9
Hentriacontane	$C_{31}H_{64}$	312/15 mm.	—	68		
Dotriacontane	$C_{32}H_{66}$	320/15 mm.	—	70		
Pentatriacontane	$C_{35}H_{72}$	344/15 mm.	—	75		
Tetracontane	$C_{40}H_{82}$	$150/10^{-5}$ mm.	—	80–81		
Pentacontane	$C_{50}H_{102}$	$200/10^{-5}$ mm.	—	92 approx.		
Hexacontane	$C_{60}H_{122}$	$250/10^{-5}$ mm.	—	99 „		
Heptacontane	$C_{70}H_{142}$	$300/10^{-5}$ mm.	—	105 „		

has since been shown to be $C_{31}H_{63}OH$; the two substances are incapable of differentiation on simple analytical grounds. Hell and Hägele prepared the hydrocarbon dohexacontane $C_{62}H_{126}$ from myricyl alcohol, through the iodide and sodium aud showed it to differ from hexacontane prepared from 1, 10-di-bromodecane and sodium.[1]

Chibnall, Piper and others have solved many problems of the structure of higher hydrocarbons, by spatial measurements of interatomic configuration, using X-ray spectra. (See under " Waxes ", Chap. VIII.)

The possibility of isomerism commences with butane, of which two forms are known, the number of possible forms can be calculated,[2, 3, 4, 5] and rapidly increases, leading to 366,319 isomers for eicosane. It is not known how many of this wide range of isomers exist in nature, for no method has been devised for distinguishing many of them, when present in small quantities.

TABLE III

Hydrocarbon	No. of possible isomers	No. of isomers (including stereoisomers)
C_4H_{10}	2	2
C_5H_{12}	3	3
C_6H_{14}	5	5
C_7H_{16}	9	11
C_8H_{18}	18	24
C_9H_{20}	35	55
$C_{10}H_{22}$	75	136
$C_{11}H_{24}$	159	388
$C_{13}H_{28}$	802	2495
$C_{14}H_{30}$	1858	7242
$C_{16}H_{34}$	10,359	—
$C_{20}H_{42}$	366,319	3,395,964
$C_{30}H_{62}$	Over 100 million	—

In addition, simple isomerism is not the only form of structural variation shown in this series, since certain of the higher hydrocarbons contain one or more asymmetric carbon atoms. Thus, of the nine possible heptanes one (3-methyl hexane) can exist in *d*- and *l*- forms ; of the eighteen octanes, three have a single asymmetric carbon and one, two such atoms :—

3-Methyl heptane	*d* and *l* forms
2, 3-Dimethyl hexane	*d* and *l* forms
2, 4-Dimethyl hexane	*d* and *l* forms
2, 2, 3-Trimethyl pentane	*d* and *l* forms
3, 4-Dimethyl hexane	*d*, *l* and meso forms

thus increasing the number of possible isomers from eighteen to twenty-four. With $C_{20}H_{42}$ (eicosane) the 366,319 structural isomers become 3,395,964 when stereoisomers are taken into account ; for heptacontane $C_{70}H_{142}$ the number is astronomical and ceases to have significance.* It must, however, be remembered that there may be some structures which, although mathematical possibilities, could not, in actual practice, exist because of steric factors ; hydrocarbons carrying an assemblage of arborescent groups as in (1) may prove impossible to produce, and may split into fragments with the carbonium or "trivalent" carbon structure. The variation of properties within an isomeric group of hydrocarbons is considerable. The normal hydrocarbon almost always has the highest boiling point followed by those secondary hydrocarbons carrying fewest branches; of two isomers with the same number of branches, that with a preponderance of heavy inner substituents has the higher boiling point. This is shown in the following table of the b. pts. of the heptanes :—

---

[1] Carothers *et al*, *J.A.C.S.*, 1930, **52**, 5279. (By the action of sodium on 1, 10-dibromodecane in moist ether, these authors obtained a series of hydrocarbons C_{20}, C_{40}, C_{50}, C_{60} and C_{70}, which were separated by distillation in a vacuum of 10^{-5} mm.)

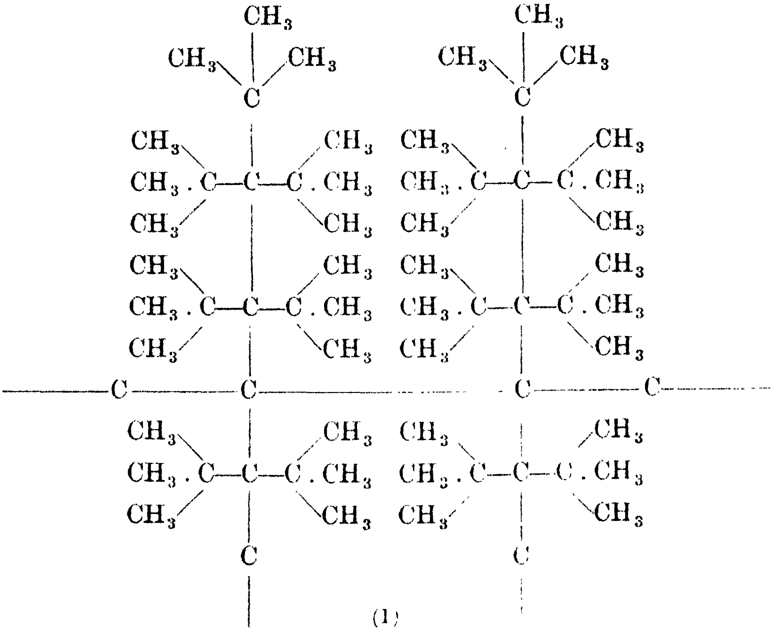
[2] *Ch. Ztg.*, 1898, **1**, 395.

[3] Blair and Henze, *J.A.C.S.*, 1932, **54**, 1098, 1538 ; 1931, **53**, 3042.

[4] Coffman, Blair and Henze, *ibid.*, 1933, **55**, 252.

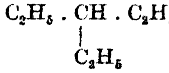
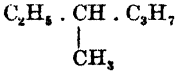
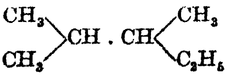
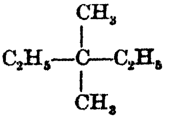
[5] Perry, *ibid.*, 1932, **54**, 2918.

* For methods of calculating the number of isomers see Henze, Blair, 1931–32 ; Perry, 1932, *loc. cit.*



(1)

TABLE IV

Structure	Name	B.P.
$CH_3(CH_2)_5CH_3$	*n*-Heptane	98·3°
 $C_2H_5 . CH(C_2H_5) . C_2H_5$	3-Ethylpentane	93·3°
 $C_2H_5 . CH(CH_3) . C_3H_7$	3-Methylhexane	91·8°
$(CH_3)_2CH . C_4H_9$	2-Methylhexane	90·0°
 $(CH_3)_2CH . CH(CH_3)(C_2H_5)$	2, 3-Dimethylpentane	89·7°
 $C_2H_5—C(CH_3)_2—C_2H_5$	3, 3-Dimethylpentane	86·0°
$(CH_3)_2CH . C(CH_3)_3$	2, 2, 3-Trimethylbutane	80·9°
$(CH_3)_2CH . CH_2 . CH(CH_3)_2$	2, 4-Dimethylpentane	80·8°
$(CH_3)_3C . C_3H_7$	2, 2-Dimethylpentane	78·9°

SYNTHETIC METHODS IN THE PARAFFIN SERIES

Pyrolytic methods of conversion and reconstitution of paraffins are discussed in the Appendix to this chapter, being more appropriate to a consideration of the petroleum industry. The purely chemical reactions leading to hydrocarbons are dealt with in this section, but it may be remarked that they do not often give pure products; the preparation of pure acyclic paraffins is often a matter of considerable difficulty.

1. *Würtz' reaction.* In outline, this method appears to be simple, sodium acting upon two molecules of an alkyl iodide to give sodium iodide and a higher hydrocarbon, for example :—

$$C_5H_{11}I + 2Na + IC_5H_{11} \longrightarrow C_{10}H_{22} + 2NaI$$

Were the reactions as simple as indicated, it would be a very valuable, as well as a unique example of three such molecules entering into simultaneous reaction. In practice, whilst it proceeds substantially along the desired lines, other substances are formed which contaminate the product, and from which it is not easily separated.

The formation of deep indigo blue substances at the surface of the sodium in Würtz' reaction first led to the suspicion that organo-sodium compounds might play an intermediate part, and Schorigin,[1] Gilman and Wright,[2] and others [3] were able to prove the existence of compounds of the type $C_5H_{11}Na$ in the reaction mixture. Würtz' reaction may therefore be written

$$C_5H_{11}I + 2Na \longrightarrow C_5H_{11}Na + NaI$$
$$C_5H_{11}I + C_5H_{11}Na \longrightarrow C_{10}H_{22} + NaI$$

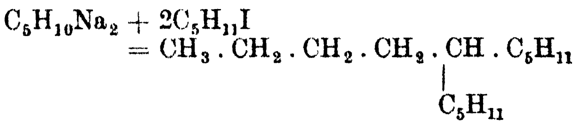
This, however, can only be part of the explanation, since the latter reaction must undoubtedly take a course leading to the temporary formation of the free radicle C_5H_{11}. Whilst two such radicles may combine to give the required product, a disproportionating action

$$2C_5H_{11} \longrightarrow C_5H_{10} + C_5H_{12}$$

can take place to some extent, leading to contamination of the product. Further, the reaction with sodium often goes further than the formation of the simple derivative, and in most cases some of the disodium derivative

$$2C_5H_{11}I + 6Na \longrightarrow 2C_5H_{10}Na_2 + 2NaI + H_2$$

is obtained. When this reacts with more alkyl iodide, the branched chain pentadecane is formed



$$\begin{array}{l} C_5H_{10}Na_2 + 2C_5H_{11}I \\ \quad = CH_3 . CH_2 . CH_2 . CH_2 . \underset{\displaystyle C_5H_{11}}{\underset{|}{CH}} . C_5H_{11} \end{array}$$

The formation of the free radicle C_5H_{10} and its direct union with a similar radicle leads to the decene $C_{10}H_{20}$, which, although only present in small traces, is difficult to remove.

The formation of these disodium derivatives was shown by Morton and Hechenbleikner,[4] who allowed sodium to react on amyl chloride and carbonated the product to give a 56 per cent. yield of caproic and butymalonic acids.

---

[1] Schorigin, *B.* 1908, **41**, 2711; **43**, 1938.

[2] Gilman and Wright, *J.A.C.S.*, 1933, **55**, 2893.

[3] Ziegler and Schäfer, *Ann.*, 1930, **479**, 150. Hückel, Kraemer and Thiele, *J. Prak. Chem.*, 1935, **142**, 207.

[4] Morton and Hechenbleikner, *J.A.C.S.*, 1936, **58**, 1697, 2599.

It is the reluctance of the sodiohydrocarbon to react with chlorides that causes the difficulty in carrying out Würtz' reaction with alkyl chlorides.

Complex as these reactions are, they appear simple by comparison with the possibilities latent in the Würtz reaction for obtaining odd-numbered hydrocarbons by the coupling of two different alkyl halides

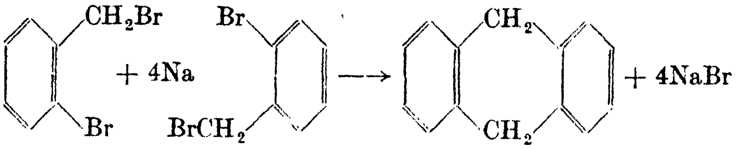
$$R_1I + 2Na + R_2I \longrightarrow R_1R_2 + 2NaI$$

in which both R_1 and R_2 are capable of leading to a group of paraffins and olefines similar to those outlined above. Purer compounds are obtained when the Würtz reaction is carried out with molecular silver. The existence of such organo-metallic derivatives as phenyl silver, AgC_6H_5 (see Vol. II) leads to the supposition that alkyl silver compounds are involved in the reactions :—

$$\begin{aligned} R_1I + 2Ag &= R_1Ag + AgI \\ R_1I + R_1Ag &= R_1 . R_1 + AgI \\ 2R_1Ag &= R_1 . R_1 + 2Ag \end{aligned}$$

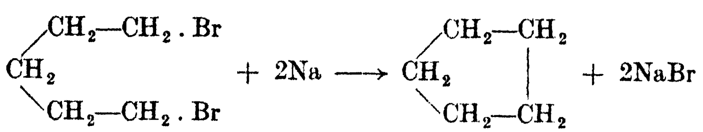
It is probable that the third reaction proceeds far more easily than the second and is responsible for the higher yield of the desired hydrocarbon.

The Würtz reaction has been applied by Fittig to alkaryl hydrocarbons ; as, for example, the formation of ethyl benzene from bromobenzene and ethyl bromide in the presence of sodium. This reaction is not confined to one side-chain ; two or more can be introduced at once with aromatic halogen compounds containing more than one halogen atom. The reaction is not, however, uniformly successful, even in the presence of catalysts such as ethyl acetate, which accelerate the more sluggish reactions. Thus, no *m*-xylene can be obtained from *m*-bromotoluene and methyl bromide, though a good yield of *p*-xylene is obtained from the *p*-bromotoluene. On the other hand, the reaction may be of considerable value in building up condensed rings, as in the case of dihydroanthracene (2) obtainable by the action of sodium on *o*-bromobenzyl bromide :—



(2)

The application of this reaction to ring closure in the preparation of *cyclo*-paraffins has been termed Freund's reaction



(3) (4)

and is moderately successful, e.g., in the preparation of *cyclo*pentane (4) from dibromopentane (3) and sodium.

Morton and Stevens[1] have suggested that the Würtz reaction may involve the formation of a 'metal halyl' either in addition to the organo-sodium or organo-silver compound or to its exclusion. They regard the halyl as a substance represented by the structure :—

$$R_1 \cdots Br \cdots Na$$

in which the sodium is associated with the halogen, but in which the bromine has a weakened affinity for the alkyl radicle, the latter thereby acquiring a residual affinity. The collision of two such activated halyl molecules would lead to :—

---

[1] Morton and Stevens, *J.A.C.S.*, 1932, **54**, 1919.

$$\begin{array}{lcl} R_1\cdots Br\cdots Na & & R_1 + BrNa \\ & \longrightarrow & | \\ R_1\cdots Br\cdots Na & & R_1 + BrNa \end{array}$$

and when in further reaction with sodium to :—

$$\begin{array}{lcl} R_1\cdots Br\cdots Na & & R_1 \quad\; BrNa \\ & & | \quad + \\ + Na & \longrightarrow & Na \end{array}$$

2. *The Grignard synthesis of paraffins.* Frankland showed that alkyl halides can react with zinc giving hydrocarbons as the final product, and in this particular instance, it was the isolation of the intermediate zinc alkyl halide that led to the recognition of this series of organo-metallic compounds. There is no doubt here as to the existence of the intermediate compound, as it can be isolated :—

$$\begin{aligned} RI + Zn &= RZnI \\ 2RZnI &= ZnR_2 + ZnI_2 \\ ZnR_2 + 2RI &= 2R—R + ZnI_2 \end{aligned}$$

The method is difficult to operate, and is almost always replaced by the more elegant Grignard reaction, in which magnesium first reacts with the halide to give the Grignard reagent :—

$$RI + Mg = RMgI$$

which, on decomposition with water, gives the simple hydrocarbon

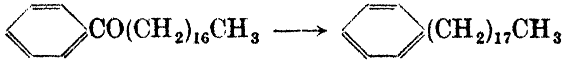
$$RMgI + H_2O = RH + MgI(OH)$$

or, on heating with a further molecule of alkyl halide, gives a moderately pure hydrocarbon of twice the carbon number :—

$$RMgI + RI = R—R + MgI_2$$

3. An alkyl halide will yield the corresponding hydrocarbon on reduction, a process which is sometimes of value. The most widely used agents are hydriodic acid in the presence of red phosphorus, the Gladstone-Tribe reagent (moist copper-zinc couple in presence of alcohol), sodium, magnesium or aluminium amalgam, and zinc dust and water under pressure. The reaction with hydriodic acid was first used by Bertholet.

The Clemmensen Reaction. The reduction of aldehydes and ketones to hydrocarbons may be accomplished by the use of amalgamated zinc, a procedure introduced by Clemmensen in 1913.[1] Mossy zinc is amalgamated by agitation with dilute mercuric chloride solution and washed by repeated decantation with water. The water is replaced by hydrochloric acid, and the substance to be reduced is added either alone or dissolved in an inert hydrocarbon solvent. Thus, octadecylbenzene is obtained from stearophenone[2]



The use of the Clemmensen reagent for the preparation of a purely aliphatic hydrocarbon is shown in the formation of *n*-heptane from heptaldehyde.[3] Acetone is reduced to propane, but some propylene and pinacol are present as by-products.[4]

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[1] Clemmensen, *Ber.*, 1913, **46**, 1838 ; 1914, **47**, 51 and 681.

[2] Johnson and Kohmann, *J.A.C.S.*, 1914, **36**, 1259.

[3] Clemmensen, *Ber.*, 1913, **46**, 1838.

[4] For a full survey of the Clemmensen reaction see "Organic Reactions", Vol. 1, p. 155 (Wiley & Sons, N. York, 1942).

4. Alcohols, aldehydes, ketones and acids can be reduced to the corresponding hydrocarbons by such violent reagents as hydriodic acid and red phosphorus (the function of the latter is to react with the iodine formed during the reaction and constantly to renew the supply of hydriodic acid). The acids can also be made to lose carbon dioxide :—

$$R.COOH \longrightarrow R.H + CO_2$$

thus giving rise to hydrocarbons with one less carbon atom. This can be brought about by heating with soda-lime, and is applicable both to aliphatic and aromatic compounds. This method is quite satisfactory with the lower acids, but with salts of the higher aliphatic acids, it is better to replace the soda-lime by sodium ethoxide, which gives a better yield of hydrocarbon.

An unusual way of effecting this elimination of carbon dioxide is that of Kolbe, who electrolysed the potassium salts of the fatty acids ; thus hexane is produced when potassium *n*-butyrate is electrolysed. The mechanism of this reaction is intricate ; the usual explanation that the anion

$$CH_3.CH_2.CH_2.COO—$$

when discharged at the anode decomposes into carbon dioxide and a free propyl radical, two of which unite to form hexane, is regarded as insufficient. Schall[1] has put forward the theory that the acid peroxide R.CO.O.OH is an intermediate stage, and this has received support from the isolation of such a peroxide by Fichter[2] during the electrolysis of potassium hexoate ; on the other hand, Walker has studied the decomposition of acetyl peroxide, and has shown that although some ethane is formed, methane is in excess ; since no methane is formed during the electrolysis of potassium acetate, the peroxide theory is only tenable on condition that the electrolytic (anodic) decomposition of the acid peroxide proceeds differently from the thermal decomposition.

THE INDIVIDUAL PARAFFINS

Methane, CH_4. As may be expected, some special methods are available for preparing the initial member of the series. Methane occurs naturally as a product of the bacterial degradation of cellulose, and as such has accumulated in the coal measures, whence considerable supplies are available ; little use is made of these. It also occurs with petroleum in the 'natural gas' fraction (see Appendix II), a source which gives rise to the main domestic gas supply in many parts of America. This natural gas, supplemented by 'cracker gas' is an important source of single carbon organic compounds. By suitable fermentation, sewage can be made to give considerable quantities of methane ; this, although not utilised as a chemical raw material, is a growing source of power, and could make a substantial contribution to industrial economy. The gases driven off in the carbonisation of coal and wood contain substantial quantities of methane.

Methane has been prepared by a number of somewhat unusual methods. Berthelot, in 1856, described its preparation from hydrogen sulphide and the vapour of carbon disulphide which were passed over glowing copper

$$2H_2S + CS_2 + 8Cu \longrightarrow CH_4 + 4Cu_2S$$

Since both carbon disulphide and hydrogen sulphide may be prepared from the elements, the reaction of Berthelot constitutes a synthesis of an organic compound from elementary sources. A similar but more modern process for the preparation of methane is the passage of steam and carbon monoxide over a nickel carbonate catalyst heated at 250–275°,

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[1] Schall, Z. *Electrochem.*, 1922, **28**, 506.
[2] Fichter and Fritz, *H. Chim. Acta*, 1923, **6**, 329.

$$4CO + 2H_2O \longrightarrow 3CO_2 + CH_4$$

There is also some evidence that methane (together with other hydrocarbons) is produced when a carbon arc is struck in hydrogen.

The preparation of methane by the action of water on aluminium carbide has often been described, and if the carbide is freshly prepared the reaction proceeds readily ; the methane contains a few per cent. of other hydrocarbons, and Moissan showed that the carbides of many metals are decomposed by water with the formation of paraffins (which, however, are usually mixed with unsaturated hydrocarbons).

Ethane occurs, like methane, in natural gas, and in the dissolved gases liberated during the distillation of petroleum. It is a substantial component of the 'cracker' gas of refining plant and of the hydrocarbon fraction of coke-oven gas. Apart from general methods already described, ethane can be prepared industrially by the continuous hydrogenation of ethylene, the ethylene-hydrogen mixture being passed over nickel.

The propanes and butanes are obtained industrially by the fractionation of 'cracker' and natural gas and a limited natural occurrence has been claimed for some of the higher paraffins, as shown in the table below.

TABLE V

$C_{22}H_{46}$	Chrysalis oil
$C_{24}H_{50}$	Pregnancy urine
$C_{25}H_{52}$	
$C_{26}H_{54}$	Chrysalis oil
$C_{27}H_{56}$	Beeswax, pregnancy urine, soot
$C_{28}H_{58}$	Chrysalis oil
$C_{29}H_{60}$	Cabbage leaves, apple and pear skin, myrrh
$C_{31}H_{64}$	Beeswax, algae, citrullus, spinach and tobacco
$C_{32}H_{66}$	Resins from brown coal
$C_{35}H_{72}$	Cotton plant
$C_{40}H_{82}$	2, 6, 10, 14, 19, 23, 27, 31-octamethyldotriacontane, or perhydrolycopene is obtained by hydrogenation of lycopene from tomatoes

THE REACTIONS OF PARAFFIN HYDROCARBONS

In general the lower paraffin hydrocarbons (up to C_{10}) are quite reactive ; their pyrolytic reactions are dealt with in the Appendix, under the heading of 'Cracking and Reformation'.

Methane with halogens, is usually stated to give progressively methyl chloride, methylene dichloride, chloroform and carbon tetrachloride, but this statement by no means covers the facts. Thus when Bedford [1] allowed chlorine and methane to stream through a glass chamber irradiated by a flaming arc, he isolated from the product the following :—

	Per cent.
Dichloromethane	35
Chloroform	35
Carbon tetrachloride	5
Chloroethanes	20

It appears that chloroethanes are produced even in the chlorination of the purest methane, and in large scale experiments, derivatives of even higher hydrocarbons have been found. Martin and Fuchs,[2] suggest that the following reaction may account for the formation of higher derivatives :—

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[1] Bedford, *J. Ind. Eng. Chem.*, 1916, **8**, 1090.

[2] Martin and Fuchs, *Z. Elektrochem.*, 1921, **17**, 150.

$$CH_2Cl_2 + CH_3Cl = ClCH_2 . CH_2Cl + HCl$$

but the intermediate formation of the free radicles CH_3— and CH_2Cl— is more probable. The progress of the chlorination is greatly influenced by the temperature, pressure and actinic conditions, and by the presence of catalysts; thus Boswell and McLaughlin [1] showed that by passing a mixture of chlorine, methane and moist nitrogen in the proportions 1 : 7 : 70 at 450° over cupric chloride-pumice, an 80 per cent. yield of methyl chloride could be obtained. On the other hand, Riesenfeld [2] was able to obtain nearly 50 per cent. of carbon tetrachloride from a mixture in which the chlorine : methane ratio was 5 : 1. The entrance of more than one chlorine atom into a paraffin hydrocarbon usually leads to a mixture of isomers ; in this connexion the rough generalisation of Herzfelder may be quoted :—

> " When into a monohalogen compound a second halogen atom is introduced it always attaches itself to that carbon atom which is situated next to the carbon atom already united with halogen. In the case of further substitutions this rule only holds for bromine, of which it is never possible, by other than violent means to attach more than one atom to each atom of carbon. On the other hand, when a third atom of chlorine is introduced, it frequently attaches itself to a carbon atom which is already united with chlorine.
>
> " Bromides that already contain one atom of bromine united with each atom of carbon cannot easily be further brominated ; chlorides, however, take up more chlorine. A normal hydrocarbon when brominated takes up as many atoms of bromine as it contains atoms of carbon. . . ."

Once the appropriate conditions have been worked out, paraffins are readily nitrated ; earlier workers used dilute nitric acid under pressure, but the yields were not good except with secondary and tertiary hydrocarbons. Modern practice is to pass the gaseous hydrocarbons through hot nitric acid and pass the mixed gases over a catalyst at 420°. The nitric acid vapour may be replaced by nitrogen peroxide. Under these conditions, although methane does not react, ethane gives both nitromethane and nitroethane in the proportions of about 1 : 3. Propane gives both 1- and 2-nitropropanes. The isomers are separable by distillation and the various nitroparaffins are prepared on a considerable scale in America, being marketed as pure substances. It is probable that they will become an important source of nitrogenous aliphatic compounds.[3]

The nitration of paraffins containing a secondary or tertiary carbon atom is much easier than that of the normal isomers. Thus a 60 per cent. yield of mono- and di-nitro compounds is obtained by boiling *n*-hexane with nitric acid (D, 1·5) for several days,[4] but acid of lower concentration (D, 1.4) will nitrate 3-methyl pentane at 50°–60° in a few hours; with fuming nitric acid, solid trinitro compounds may be obtained from 3-methylpentane by raising the temperature (mainly 2, 2, 3-trinitro-3-methylpentane).

Quaternary hydrocarbons R_4C are nitrated only with the utmost difficulty or not at all ; on the other hand, di-tertiary paraffins are almost instantaneously nitrated, even at room temperature, e.g., 2, 3-dimethylbutane gives a mixture of the 2-nitro and 2, 3-dinitro compounds :—

$$(CH_3)_2 . CH . CH(CH_3)_2 \longrightarrow (CH_3)_2 . C(NO_2) . CH . (CH_3)_2 \longrightarrow (CH_3)_2 . C(NO_2) . C(NO_2)(CH_3)_2$$

---

[1] Boswell and McLaughlin, *Can. J. Res.*, 1929, **1**, 240.

[2] Riesenfeld, U.S.P. 1, 455,508, 1923.

[3] Haas, *Ind. Eng. Chem.*, 1936, **28**, 339.

[4] Worstall, *Amer. Chem. J.*, 1898, **20**, 202.

The use of dilute nitric acid at higher temperatures enables the alkyl side-chain of an alkaryl hydrocarbon to be nitrated preferentially, thus *o*-xylene and mesitylene give respectively *o*-tolylnitromethane and 3, 5-xylylnitromethane.

The paraffins can be sulphonated directly, using oleum or chlorsulphonic acid. It is not, however, easy to isolate definite compounds from the reaction mixtures, since the paraffin sulphonic acids are somewhat intractable substances. The crude sulphonates are valuable detergents, being able to exercise their scouring properties in hard waters; for this purpose, however, isolation of definite individual sulphonates is unnecessary. A crude mixture of sulphonates, known as ' mahogany sulphonates ', is widely used as a textile assistant and wetting out agent.

One of the most interesting reactions of the paraffins is their oxidation. With lower members of the series much aldehyde is obtained. The oxidation of hydrocarbon vapours has been investigated by Bone and his co-workers, by the passage of mixture of pure oxygen and the hydrocarbon vapour through packed, heated tubes. It appears that methane and ethane give aldehydes as the first stage of oxidation, by the sequence of reactions

$$\text{A.}\quad CH_4 \xrightarrow[+O_2]{} CH_2(OH)_2 \xrightarrow[-H_2O]{} H\,.\,CHO + H_2O.$$

$$\text{B.}\quad C_2H_6 \xrightarrow[+O_2]{} CH_3CH(OH)_2 \xrightarrow[-H_2O]{} CH_3\,.\,CHO \xrightarrow[O_2]{}$$

$$\begin{array}{l} CH_2OH \\ | \\ COOH \end{array} \longrightarrow HCHO + CO + H_2O$$

Actually, 80 per cent. of the ethane was recovered as formaldehyde. Apparently, the formaldehyde then decomposes into carbon monoxide and hydrogen.

The oxidation of higher hydrocarbons is very readily accomplished by air or oxygen at low temperatures (100°–180°) and in the absence of catalysts. The reaction is applicable equally to the individual hydrocarbons or to commercial mixtures such as kerosene. The products are a series of carboxylic acids which are to a large extent little known as individual pure substances, e.g.

$C_{11}H_{22}O_2$	Undecyclic acid
$C_{13}H_{26}O_2$	Tridecyclic acid
$C_{15}H_{30}O_2$	Pentadecyclic acid
$C_{17}H_{34}O_2$	Margaric acid
$C_{19}H_{38}O_2$	Nonadecyclic acid
$C_{24}H_{48}O_2$	Lignoceric acid

in which the lesser known, odd-numbered carbon chains predominate. In addition, the higher alcohols and some ketones of the stearone group are produced.

Gränacher used N_2O_4 as the oxidant, and by an examination of the oxidation of undecane showed that the mechanism involves loss of two carbon atoms, pelargonic acid $C_9H_{18}O_2$ being the chief product. Such reactions offer the possibility of preparing ' synthetic ' fats or soaps (better termed ' artificial ' fats and soaps). The disadvantages of such products are (1) the dark colour of the material produced which is only with extreme difficulty removed by bleaching, (2) the fact that splitting of the molecule as well as oxidation takes place leading to acids of the capric-lauric group which have an unpleasant smell and taste, (3) the more usual palmitic and stearic acids are present only in small quantity (if at all), and the physical properties of the mixtures obtained are, therefore, quite different from those of ordinary fatty acids and soaps; the same is true of the glyceryl esters of these acids—the ' artificial ' fats.

THE OLEFINES

The general phenomena of unsaturation are discussed in a chapter of Vol. III ; it is sufficient to state here that the olefine hydrocarbons are obtained by the introduction of one or more double bonds into a paraffin structure. They are, therefore, more numerous than the paraffins, since each paraffin structure from C_4 offers several positions into which the double bond may be introduced. In a previous section it was remarked that the hydrocarbon $C_{20}H_{42}$, eicosane, had 366,319 isomers, or 3,395,964 isomers, taking stereoisomerides into account; the corresponding olefine $C_{20}H_{40}$ has over 100,000,000 isomeric forms, as not only has the position of the double bond to be taken into account, but also geometrically isomeric variants. Experiment shows that there is a fairly constant proportion maintained between the hydrogen and deuterium in hydrocarbons ; there must therefore be an astronomically large number of variant ways in which one or more deuterium atoms can replace the hydrogens of the 10^8 isomeric forms of $C_{20}H_{40}$ (see also Vol. II).

Unsaturated hydrocarbons have a limited natural occurrence in petroleum, but are largely found in ' cracked spirit ', where they contribute to the raising of the ' octane rating '. Some ethylene and propylene are also to be found in coke-oven gas from which it is practicable to recover them as ethylene and propylene dichlorides or as diethyl and dipropyl sulphates (q.v.).

OLEFINIC HYDROCARBONS

The following methods serve for the preparation of olefinic hydrocarbons :—

1. *The Dehydration of Alcohols.* This decomposition may be brought about by sulphuric or phosphoric acids and to a limited extent by fused zinc chloride. The best reagent is orthophosphoric acid of density 1·75, heated to 210°, through which a stream of the alcohol is allowed to flow by a capillary tube. The reaction can also be brought about by passing the vapour of the alcohol over alumina heated to 530–550° ; apparently, the first decomposition is the formation of an ether :—

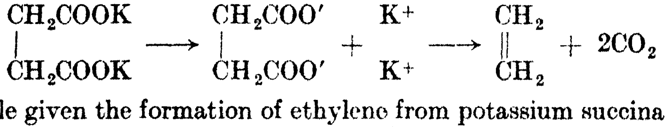
$$2C_2H_5OH \longrightarrow C_2H_5 . O . C_2H_5 + H_2O$$

followed by decomposition of this into the hydrocarbon :

$$C_2H_5 . O . C_2H_5 \longrightarrow 2C_2H_4 + H_2O$$

A similar decomposition is produced by pure precipitated silica at 280°. Higher alcohols are easily dehydrated by warming with zinc chloride, e.g., amyl alcohol is converted in this way to amylene.

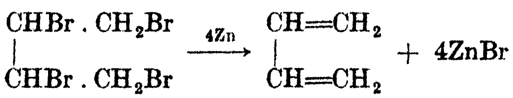
2. A method similar to the Kolbe synthesis of paraffins has been applied to the olefines, namely, the electrolysis of the potassium salts of dibasic acids ; in



$$\begin{array}{l}CH_2COOK\\|\\CH_2COOK\end{array} \longrightarrow \begin{array}{l}CH_2COO'\\|\\CH_2COO'\end{array} + \begin{array}{l}K^+\\ \\K^+\end{array} \longrightarrow \begin{array}{l}CH_2\\\|\\CH_2\end{array} + 2CO_2$$

the example given the formation of ethylene from potassium succinate is shown.

3. Many methods involve the removal of halogen atoms, or the elements of a molecule of halogen acid from a saturated halogen compound. Thus, ethyl bromide, with alcoholic potash, yields very little ethylene. On the other hand, when butadiene tetrabromide (2) is heated with an alcoholic suspension

(2) 

$$\begin{array}{l}CHBr . CH_2Br\\|\\CHBr . CH_2Br\end{array} \xrightarrow{4Zn} \begin{array}{l}CH{=}CH_2\\|\\CH{=}CH_2\end{array} + 4ZnBr$$

of zinc-dust, the whole of the bromine is removed, yielding butadiene itself. An alternative method is to pass the vapour of the halogen compound over heated lime. The reaction is less satisfactory in very simple cases than with compounds of higher molecular weight owing to the formation of ethers. Thus a reaction which might be expected to proceed almost entirely

$$C_nH_{2n+1}Br + KOH \longrightarrow KBr + CnH_{2n} + H_2O$$

also proceeds to some extent according to :—

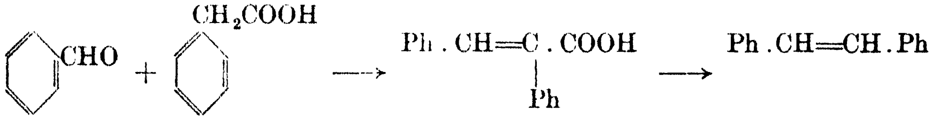
$$2C_nH_{2n+1}Br + 2KOH = (C_nH_{2n+1})_2O + 2KBr + H_2O$$

The most satisfactory explanation of this behaviour is that given by Nef, who supposes that the first stage is the formation of ethylidene $CH_3CH{=}$, or one of its homologues, which being intensely reactive, either rearranges to an olefine or reacts with alcohol to form the ether, as in :—

$$\begin{aligned}&(a)\ CH_3CH{=} \longrightarrow CH_2{=}CH_2\\&(b)\ CH_3CH{=} + C_2H_5OH \longrightarrow (C_2H_5)_2O\end{aligned}$$

The proportions of olefine resulting will depend on the reaction constants for (*a*) and (*b*) above ; for simple substances K_a and K_b are of the same order but with increasing molecular weight the first reaction is more rapid and the olefine preponderates. The acceptability of this explanation depends on the probability of existence of the free radicle alkylidene. This is more fully dealt with in Chapter 5, Vol. III, but it is worthy of mention here that methylene $CH_2{=}$ can exist for a short time and its existence has been demonstrated by Rice in 1933 during the cracking of diazomethane.

4. An interesting preparation of semi-aromatic hydrocarbons of this series is the Perkin reaction with elimination of carbon dioxide. Thus, when benzaldehyde (5) is condensed with phenylacetic acid (6), as in the Perkin reaction, the intermediate acid (7) is unstable



(5) (6) (7)

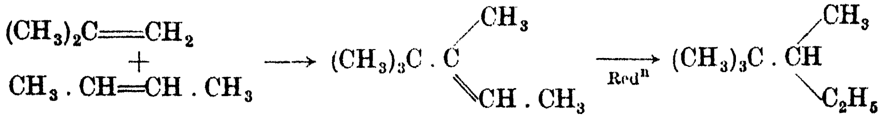
and if heated in an oil-bath loses the elements of carbon dioxide with the formation of an unsaturated hydrocarbon. In the example quoted, diphenylethylene (stilbene) is obtained.

5. One prolific method by which new olefines are produced is due to their pronounced tendency towards dimerisation. Thus, dimerisation of *iso*-butene by absorption in 65 per cent. sulphuric acid at 10–20° leads to a solution which, on heating, gives an oil containing upwards of 70 per cent. of a dimeric *iso*-butene (8), which can be hydrogenated to *iso*-octane by catalytic means. The substance produced is substantially 2, 2, 4-trimethylpentane, whilst the dimeric *iso*-butene is a mixture of 2, 2, 4-trimethylpentene-3 and 2, 4, 4, trimethylpentene-1. Some indication of the course of this mechanism is given by assuming the addition to take place in part, thus :—

$$\begin{array}{c}(CH_3)_2C{=}CH_2\\+\\(CH_3)_2C{=}CH{-}H\end{array} \longrightarrow \underset{(8)}{(CH_3)_2C{=}CH\,.\,C(CH_3)_3}$$

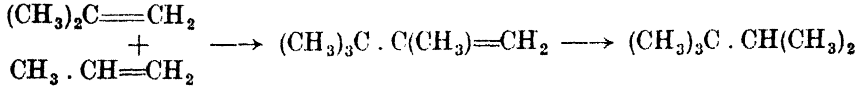
but it is probable that an active intermediate radicle is formed, since whilst *iso*-butene gives a dimer and a tetramer, neither the dimer nor the tetramer give long chain hydrocarbons under conditions which prove quite favourable for such formation direct from *iso*-butene. (See also two papers by E. Bergmann and by W. J. Sparks, R. Rosen and P. K. Frolich in the Faraday Society Discussion.)

The reaction can be extended to 'mixed dimerisations' as between butene and *iso*-butene :—



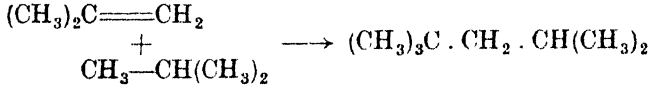
(9)

leading after hydrogenation to 2, 2, 3-trimethylpentane (9). It may be added that the work of Ipatiev and Hænsel has extended this reaction to the addition of propylene to *iso*butene, to give 2, 2, 3-trimethyl butene-3, which hydrogenates readily to 2, 2, 3-trimethylbutane, 'triptane', an aviation fuel component with an octane rating of 150. The reaction proceeds :—



$$\begin{matrix}(CH_3)_2C{=}CH_2\\ +\\ CH_3 . CH{=}CH_2\end{matrix} \longrightarrow (CH_3)_3C . C(CH_3){=}CH_2 \longrightarrow (CH_3)_3C . CH(CH_3)_2$$

Further, it may be added here that *iso*-butene will add quite easily to *iso*-butane, leading directly to *iso*-octane :—



$$\begin{matrix}(CH_3)_2C{=}CH_2\\ +\\ CH_3{-}CH(CH_3)_2\end{matrix} \longrightarrow (CH_3)_3C . CH_2 . CH(CH_3)_2$$

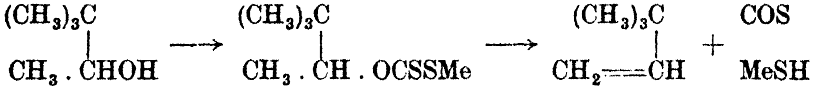
The reaction takes place readily in the presence of sulphuric or hydrofluoric acids, and is reasonably quantitative. This process, referred to as 'alkanation' in the petroleum industry, gives rise to an industrial method of manufacturing *iso*-octane for aviation fuel.

6. A useful method of preparing 1-olefines free from isomers is that of Brooks, in which methyl magnesium bromide and an unsaturated bromide are heated together, e.g.

$$CH_2{=}CH . CH_2Br + CH_3MgBr \longrightarrow CH_2{=}CH . CH_2 . CH_3 + MgBr_2$$

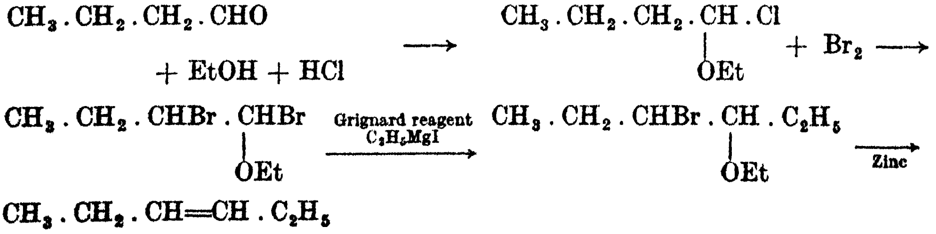
For the preparation of some of the higher olefines, where the dehydration of the appropriate alcohol does not yield the correct isomer, the two methods following are often successful.

The first, introduced by Tschugaev in 1899, consists in decomposing the xanthate of an alcohol. Thus, 2, 2-dimethylbutanol-3 (pinacolyl alcohol) (10) yields a xanthate with alkali and carbon disulphide which can be methylated by dimethyl sulphate (11). On heating, the methyl xanthate decomposes to give 3, 3-dimethylbutene-1 (12), methylthiol and carbon oxysulphide.



$$\underset{(10)}{\begin{matrix}(CH_3)_3C\\ |\\ CH_3 . CHOH\end{matrix}} \longrightarrow \underset{(11)}{\begin{matrix}(CH_3)_3C\\ |\\ CH_3 . CH . OCSSMe\end{matrix}} \longrightarrow \underset{(12)}{\begin{matrix}(CH_3)_3C\\ |\\ CH_2{=}CH\end{matrix}} + \begin{matrix}COS\\ \\ MeSH\end{matrix}$$

The second method, the 'β-bromoether synthesis', depends on the following reactions :—



$$\begin{matrix}CH_3 . CH_2 . CH_2 . CHO\\ + EtOH + HCl\end{matrix} \longrightarrow \begin{matrix}CH_3 . CH_2 . CH_2 . CH . Cl\\ |\\ OEt\end{matrix} + Br_2 \longrightarrow$$

$$\begin{matrix}CH_3 . CH_2 . CHBr . CHBr\\ |\\ OEt\end{matrix} \xrightarrow[C_2H_5MgI]{\text{Grignard reagent}} \begin{matrix}CH_3 . CH_2 . CHBr . CH . C_2H_5\\ |\\ OEt\end{matrix} \xrightarrow{\text{Zinc}}$$

$$CH_3 . CH_2 . CH{=}CH . C_2H_5$$

(hexene-3)

Several heptenes and octenes, hitherto unknown, have been prepared by these reactions.

The main physical properties of the simple olefines are contained in the table below :—

TABLE VI

The Olefines

	M.P.	B.P.	D_4^{20}
C_2H_4 Ethylene	— 169°	— 103°	0·6104/–102·4°
C_3H_6 Propylene	— 185°	— 47·7°	0·6104/–47·7°
C_4H_8 *n*-Butene-1		— 6·47°	0·6255/–6·47°
C_4H_8 *n*-Butene-2 (cis)	— 139·3°	+ 3·7°	
C_4H_8 *n*-Butene-2 (trans)	— 105·8°	1°	
C_5H_{10} *n*-Pentene-1		— 30·1°	0·6429
C_5H_{10} *n*-Pentene-2 (cis)		37°	0·6503
C_5H_{10} *n*-Pentene-2 (trans)		35·85°	0·6482
C_6H_{12} *n*-Hexene-1	— 138°	— 63·5°	0·6747
C_7H_{14} *n*-Heptene-1	— 119°	93·1°	0·6976
C_8H_{16} *n*-Octene-1	— 104°	122·5°	0·7159
C_9H_{18} *n*-Nonene-1		146°	0·7308
$C_{10}H_{20}$ *n*-Decene-1		171°	0·743
$C_{11}H_{22}$ *n*-Undecene-1		84°/18 mm.	0·763
$C_{12}H_{24}$ *n*-Dodecene-1	— 31°	213° ; 96°/15 mm.	0·760
$C_{13}H_{26}$ *n*-Tridecene-1	— 13°	233° ; 102°/10 mm.	0·767
$C_{14}H_{28}$ *n*-Tetradecene-1	— 12°	127°/15 mm.	0·772
$C_{15}H_{30}$ *n*-Pentadecene-1	— 3°	247° ; 144°/15 mm.	0·778
$C_{16}H_{32}$ *n*-Hexadecene-1 (Cetene)	+ 4°	275° ; 155°/15 mm.	0·7835
$C_{18}H_{36}$ *n*-Octadecene-1	18°	179°/15 mm.	0·791
* $C_{26}H_{52}$ *n*-Hexacosene-1	52°	200–205°/2 mm.	
* $C_{31}H_{62}$ *n*-Hentriacontene-1	64°	233°/1·5 mm.	

* Cerotene, a structurally indeterminate hexacosene $C_{26}H_{52}$, is obtained by the destructive distillation of Chinese wax, and melene, a triacontene $C_{30}H_{60}$ from beeswax and lignite tars. It is not yet certain that these bodies contain the normal chain.

Ethylene is found in natural and coke-oven gases, from which it may be separated by condensation and fractionation of the liquid hydrocarbons under pressure. The bulk of the ethylene used in industry is, however, obtained by cracking propane

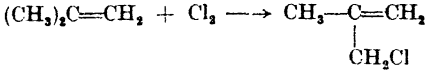
$$CH_3 . CH_2 . CH_3 \longrightarrow CH_2{=}CH_2 + CH_4$$

Vast quantities of raw natural gas or stabiliser gas from cracking units are available in the petroleum industry, and these may contain up to 80 per cent. of propane. Pyrolysis at 700° substantially converts the gas to ethylene and methane, which may be separated by liquefaction and fractionation or by taking advantage of the enhanced reactivity of ethylene in comparison with that of methane. This ethylene constitutes the raw material for a very considerable industry, some of the ramifications of which are to be seen in Table VII (compiled by A. E. Dunstan) facing page 80.

At the same time some propylene and butene are produced, although in much smaller quantity ; they are, however, valuable, and their industrially important compounds are also indicated in the Table above.

There is much information available concerning the homologues of ethylene ; their reactions are in many ways similar to those of ethylene ; some of the more prominent points are given in the Table below :—

TABLE VIII—Some Properties of the Olefines

<table>
<tr><th></th><th>Preparation and occurrence</th><th>Properties and reactions</th><th>Uses</th></tr>
<tr><td>**Propylene**</td><td>Usual methods and by heating glycerol and zinc dust
Pure propylene is obtained by Ipatiev's reaction ; propyl alcohol over heated alumina</td><td>
<table>
<tr><th></th><th colspan="3">Bromination :</th></tr>
<tr><th></th><th>Propylene dibromide</th><th colspan="2">Tribromopropane</th></tr>
<tr><th></th><th></th><th>1, 2, 2</th><th>1, 1, 2</th></tr>
<tr><td></td><td>Per cent.</td><td>Per cent.</td><td>Per cent.</td></tr>
<tr><td>Pure bromine</td><td>90</td><td>4</td><td>—</td></tr>
<tr><td>,, Br$_2$—Fe</td><td>40</td><td>40</td><td>17</td></tr>
<tr><td>FeBr$_3$ or AlBr$_3$</td><td>55</td><td>8</td><td>33</td></tr>
</table>
Hypochlorous acid gives 1-chloropropanol-2
More reactive than C_2H_4 ; more easily oxidised and absorbed by sulphuric acid ; polymerises more readily, gives a larger (25 per cent.) proportion of aromatics on pyrolysis</td><td>Manufacture of—
iso-propanol,
propandiol,
propanone,
iso-propyl acetate,
iso-propyl ether,
propylene oxide,
propylene chlorhydrin,
glycerol
Pure propylene can be used as an anæsthetic</td></tr>
<tr><td>**Butenes**</td><td>All four are known
$CH_2{=}CH \cdot CH_2CH_3$ Butene-1 $CH_3CH{=}CHCH_3$ *cis*- and *trans*-Butene-2
$(CH_3)_2C{=}CH_2$ Methylpropene
Butene-1, *cis*-Butene-2, *trans*-Butene-2 $\}$ from cracker gas
Methylpropene $\{$ can be washed from cracker gas by dilute sulphuric acid
The *cis*- and *trans*- forms of butene-2 were obtained for structural identification from angelic and tiglic acids (q.v.)</td><td>
<table>
<tr><th></th><th>B.P.</th></tr>
<tr><td>Butene-1</td><td>— 6·47°</td></tr>
<tr><td>*cis*-Butene-2</td><td>— 3·7°</td></tr>
<tr><td>*trans*-Butene-2</td><td>— 1·0°</td></tr>
<tr><td>Methylpropene</td><td>— 6·6°</td></tr>
</table>
Butene-1 and butene-2 give 2-bromo butane with HBr ; methylpropene gives *ter*-butyl bromide
Chlorination of methylpropene yields the substitution product, methallyl chloride, not the addition product
$$(CH_3)_2C{=}CH_2 + Cl_2 \longrightarrow CH_3{-}\underset{\displaystyle CH_2Cl}{\underset{|}{C}}{=}CH_2$$
Methallyl compounds are produced industrially in large quantities from cracker gas methylpropene in this way. Some *iso*-crotyl chloride (2-Methyl-3, chloropropene-2) is also formed
(See also Chap. IV)</td><td>Manufacture of—
butanol-1,
butanol-2,
trimethyl carbinol,
butyl esters,
butylene oxide,
methallyl compounds
Condensation with butane to give *iso*-octane
Dimerisation followed by hydrogenation to *iso*-octane</td></tr>
</table>

Pentenes	All possible isomerides are known, viz.: I. Pentene-1, $CH_2{=}CH . CH_2CH_2CH_3$, b.p. 30° II. Pentene-2, $CH_3CH{=}CH . CH_2CH_3$, b p. 36·4° III. 2-Methylbutene-1, $CH_2{=}C(CH_3)CH_2CH_3$, b.p. 32° IV. 2-Methylbutene-2 $(CH_3)_2C{=}CH . CH_3$, b.p. 38·4° V. 3-Methylbutene-1 $CH_2{=}CH . CH(CH_3)_2$, b.p. 20·1° *Preparation* *Dehydration of alcohols* $\left.\begin{array}{l}\text{Pentanol-1}\\ \text{Pentanol-2}\end{array}\right\}\left\{\text{I + II}\right.$ 2-Methylbutanol-1 → I, II, IV 3-Methylbutanol-1 → IV + a few per cent. V 2-Methylbutanol-2 → III and IV	The reactions of the pentenes are normal, and do not diverge from what may be expected save in the following points: Pentene-1, in most solvents disobeys Markownikov's Rule, only *n*-amyl bromide being obtained. On heating 3-methylbutene-1 and 2-methylbutene-1 they rearrange to 2-methylbutene-2. Both 2-methylbutene-1 and 2-methylbutene-2 are extremely reactive: on the other hand, 3-methylbutene-1 is sluggish and unreactive, especially towards halogen acids	The manufacture of amyl compounds generally
Hexenes	All thirteen forms are known. The pyrolysis of pinacolyl acetate yields 3, 3-Dimethylbutene-1 $(CH_3)_3 . C . CH{=}CH_2$	Tetramethylethylene shows some spatial hindrance, but is capable of polymerisation with ease Two are of particular interest—2, 3-dimethylbutene-2 (tetramethylethylene) on account of its having no hydrogen atoms on the carbons of the ethylene bond. It, therefore, forms a true nitroso compound (blue in colour) The other point of interest lies in the *cis-* and *trans-* isomers of 3-methylhexene-2, which boil sufficiently far apart to enable their separation by fractionation (*cis-* b. 66°; *trans-*, b. 69°)	

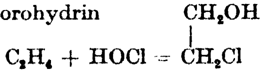
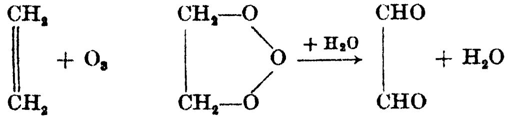
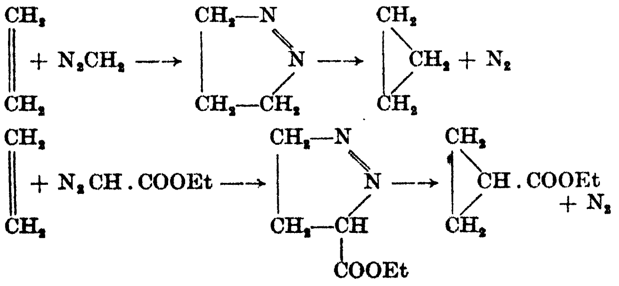
TABLE VIII—SOME PROPERTIES OF THE OLEFINES (*continued*)

	Preparation and occurrence	Properties and reactions	Uses
Heptenes	All 27 are known, many have been prepared by the Tschugaev reaction, or the β-bromo-ether synthesis. The following are among the commoner isomers : Heptene-2, $CH_3 . CH{=}CH(CH_2)_3CH_3$, b.p. 98·3° Heptene-1, $CH_2{=}CH . (CH_2)_4CH_3$, b.p. 94·9° 2-Methylhexene-2 $(CH_3)_2 . C{=}CH(CH_2)_2CH_3$, b.p. 94·5° 2-Methylhexene-1 $CH_2{=}C(CH_3)(CH_2)_3CH_3$, b.p. 91·3° 2 : 3-Dimethylpentene-2, $(CH_3)_2C{=}C(CH_3)CH_2CH_3$, b.p. 91°		
Octenes	23 of the 66 possible forms are known		
Cetene (hexadecene)	$C_{16}H_{32}$ obtained with higher olefines from cetyl alcohol	Was originally used for the standardisation of Diesel fuel knock ratings Has now been replaced by hexadecane (cetane)	

REACTIONS OF OLEFINES

The reactions of olefines are largely concerned with addition to the double bond. The presence of unsaturation, although conventionally signified by a double bond, is in reality a source of weakness, forming the centre of attack by reagents, which may either add on to the unsaturated group, or fracture the compound between the carbon atoms so joined. The additive reactions may be summarised thus :—

TABLE IX

Reagent	Type of compound produced
Chlorine	$C_2H_4 + Cl_2 \longrightarrow C_2H_4Cl_2$ Dichlorohydrocarbon
Bromine	$C_2H_4 + Br_2 \longrightarrow C_2H_4Br_2$ Dibromohydrocarbon
Iodine chloride or bromide	$C_2H_4 + ICl \longrightarrow C_2H_4ICl$
Halogens in the presence of water	Halohydrins $C_2H_4 + H_2O + Cl_2 \longrightarrow C_2H_4(OH)Cl + HCl$
Halogen acid	Simple alkyl halide $C_2H_4 + HBr = C_2H_5Br$
Hypochlorous acid	The chlorohydrin  $C_2H_4 + HOCl = \begin{array}{l} CH_2OH \\ \vert \\ CH_2Cl \end{array}$
Potassium permanganate or barium chlorate	The elements of hydrogen peroxide add across the double bond, to give a glycol. This often breaks down into simpler products
Ozone	Certain olefinic compounds add on one molecule of ozone for each double bond, giving ozonides * 
Hydrogen	In the presence of catalysts, olefines may be quantitatively reduced to the saturated hydrocarbon $C_2H_4 + H_2 = C_2H_6$
Diazomethane	Many compounds containing double bonds react with diazomethane to give ring compounds which lose nitrogen spontaneously to form *cyclo*-propane derivatives
Diazoacetic ester	Reacts similarly to diazomethane, viz. : 

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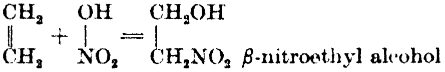
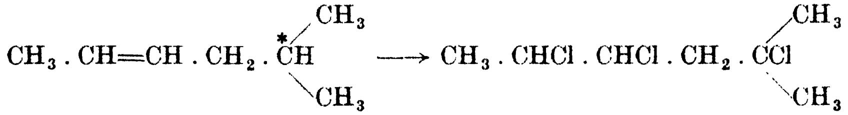
* Not all ozonides have the structure shown ; see p. 89.

TABLE IX—*continued*

Reagent	Type of compound produced
Sulphuric acid	Ethylene and propylene are readily absorbed by sulphuric acid and under appropriate conditions the dialkyl ester may be obtained : $2C_2H_4 + H_2SO_4 \longrightarrow (C_2H_5)_2SO_4$ The alkyl hydrogen sulphate may also be obtained : $C_2H_4 + H_2SO_4 \longrightarrow (C_2H_5)HSO_4$
Nitrosyl chloride	$R . CH{=}CH_2 + NOCl \longrightarrow R . CHCl . CH_2NO$
Fuming nitric acid	 $\begin{array}{l}CH_2\\ \Vert\\ CH_2\end{array} + \begin{array}{l}OH\\ \vert\\ NO_2\end{array} = \begin{array}{l}CH_2OH\\ \vert\\ CH_2NO_2\end{array}$ β-nitroethyl alcohol
Water	The direct addition of water in the presence of catalysts gives alcohols $C_2H_4 + H_2O \longrightarrow C_2H_5OH$
Oxygen	Lenter [1] has shown that oxygen will add directly across the double bond, yielding an epoxy compound, e.g., ethylene oxide $2C_2H_4 + O_2 \longrightarrow 2C_2H_4O$

Olefines and Halogens. Although addition to the double bond takes place to a substantial extent, some substitution takes place at the same time especially if the hydrocarbon carries a tertiary carbon atom as at * in the 2-methylhexene-4, below, which gives quite an appreciable amount of 2, 4, 5-trichloro-2-methylhexane on chlorination.



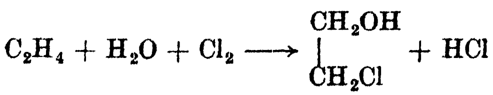
$$CH_3 . CH{=}CH . CH_2 . \overset{*}{C}H\begin{array}{l}\diagup CH_3\\ \diagdown CH_3\end{array} \longrightarrow CH_3 . CHCl . CHCl . CH_2 . CCl\begin{array}{l}\diagup CH_3\\ \diagdown CH_3\end{array}$$

Even with ethylene itself some 1, 1, 2-trichloroethane is obtained.

Ethylene dichloride is obtained almost exclusively by the action of chlorine on crude ethylene under controlled conditions, although it is possible to use hydrogen chloride and air, in the presence of a copper catalyst at 300°. By using higher temperatures and catalysts the chlorination of ethylene can be made to yield substantial proportions of trichloroethane and tetrachloroethane. Thus, at 60° in the presence of antimony the product is mainly 1, 1, 2-trichloroethane, whilst at higher temperatures tetrachloroethane is obtained ; finally, at 300–350°, and in the presence of activated carbon, hexachloroethane is obtained.

With bromine, the latitude of conditions leading to ethylene dibromide is much greater than with chlorine, as substitution is more difficult. Ethylene will combine with iodine ; directly, in sunlight, as pointed out by Faraday in 1820, or when passed into a paste of iodine and alcohol (Semenov 1864).

When halogens and ethylene react in the presence of water, the chlorohydrin or bromohydrin is produced almost exclusively :—

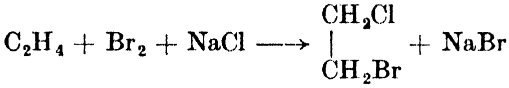


$$C_2H_4 + H_2O + Cl_2 \longrightarrow \begin{array}{l}CH_2OH\\ \vert\\ CH_2Cl\end{array} + HCl$$

---

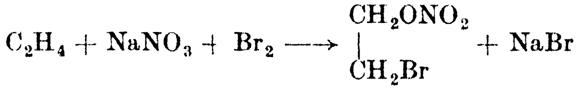
[1] Lenter, *J.A.C.S.*, 1931, **53**, 3787 ; 1932, **54**, 1830.

This constitutes the industrial process for making bulk supplies of ethylene chlorohydrin, for the manufacture of ethylene oxide. The reaction is substantially quantitative, and gives very little of the dihalide. If, however, a salt is present in the aqueous phase, the anion may take part in the reaction. Thus, bromine and sodium chloride yield ethylene chlorobromide (1, 2-chlorobromoethane).

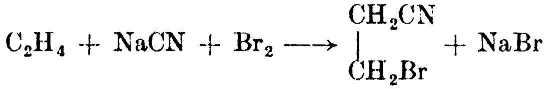


$$\mathrm{C_2H_4 + Br_2 + NaCl \longrightarrow \begin{matrix} CH_2Cl \\ | \\ CH_2Br \end{matrix} + NaBr}$$

This is true of non-halogen anions, e.g., nitrates and cyanides which react :—



$$\mathrm{C_2H_4 + NaNO_3 + Br_2 \longrightarrow \begin{matrix} CH_2ONO_2 \\ | \\ CH_2Br \end{matrix} + NaBr}$$



$$\mathrm{C_2H_4 + NaCN + Br_2 \longrightarrow \begin{matrix} CH_2CN \\ | \\ CH_2Br \end{matrix} + NaBr}$$

In the reactions discussed above, ethylene has been used as an example, but the reactions are not restricted to the initial member of the series, and propylene and the butenes react easily in a similar manner ; as usual, the reactions become more difficult to bring about with members of the series higher than decene, but the majority of the additions can be accomplished by the use of more stringent conditions.

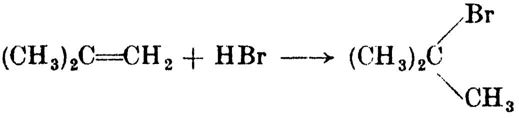
When addition of a halogen acid to a double bond takes place in an unsymmetrical unsaturated compound. two products are theoretically possible :—

(i) $\mathrm{R\,.\,CH{=}CH_2 + HBr \longrightarrow R\,.\,CH_2\,.\,CH_2Br}$

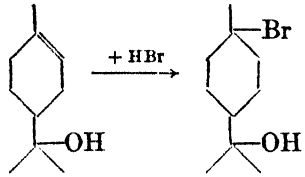
(ii) $\mathrm{R\,.\,CH{=}CH_2 + BrH \longrightarrow R\,.\,CHBr\,.\,CH_3}$

Actually, the latter of these two would largely predominate, and would be, in many cases, the sole product. This effect has been generalised by Markownikov (1870) (" Markownikov's Rule ") in the statement that " when a molecule of halogen acid unites with an unsymmetrical unsaturated compound the halogen usually attaches itself to the carbon atom carrying the smaller number of hydrogen atoms or the larger number of alkyl groups ". Two examples are given below :—

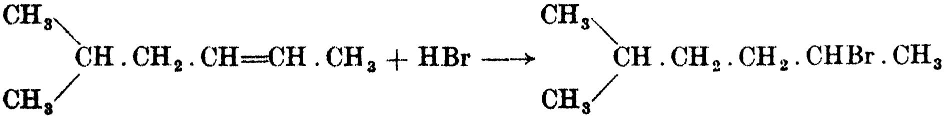
(1)



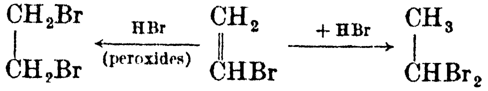
(2)



Although the rule is generally true, it is not by any means without exception. Saytzew-Wagner's extension of the Markownikov rule covers instances where unsymmetrical unsaturated compounds add halogen acids across a bond carrying an equal number of hydrogen atoms—as in



They predict that the halogen will add to the carbon adjacent or nearest to a terminal methyl group. Where other substances are present, either as solvents or otherwise, these rules are not strictly obeyed. Thus, in glacial acetic acid propylene yields a preponderance of *n*-propylbromide, and pentene-1, and hexene-1 yield the *n*-bromides exclusively under similar conditions and in the presence of peroxides the predictions of Markownikov's rule are reversed, and *n*-halides obtained. Thus, Kharasch was able to demonstrate that vinyl bromide gave the unsymmetrical dibromoethane when peroxides were absent; in their presence the symmetrical product is largely formed :—



$$\begin{array}{c} CH_2Br \\ | \\ CH_2Br \end{array} \xleftarrow[\text{(peroxides)}]{HBr} \begin{array}{c} CH_2 \\ \| \\ CHBr \end{array} \xrightarrow{+HBr} \begin{array}{c} CH_3 \\ | \\ CHBr_2 \end{array}$$

Olefines and Sulphuric Acid.—The reaction may take place in two stages, the first resulting in an alkyl acid sulphate, e.g. :—

$$C_2H_4 + H_2SO_4 \longrightarrow C_2H_5 . O . SO_3H$$

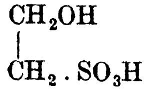
but under suitable conditions with ethylene and lower members of the series, the reaction can be extended. Thus, ethylene itself yields diethylsulphate, a valuable ethylating agent.

$$C_2H_4 + H_2SO_4 \longrightarrow (C_2H_5)_2SO_4$$

The former reaction is not so easy to bring about with ethylene as with propene and butene, but is catalysed by silver or nickel sulphates. By decomposing the ethyl hydrogen sulphate with steam, ethanol can be obtained, this constituting an industrial process for its production :—

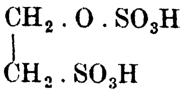
$$C_2H_5OSO_3H + H_2O \longrightarrow C_2H_5OH + H_2SO_4$$

If sulphuric acid containing sulphur trioxide is used for the absorption of ethylene, a series of compounds may be obtained, according to the amount of free sulphur trioxide :—



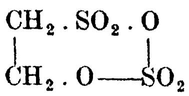
$$\begin{array}{l} CH_2OH \\ | \\ CH_2 . SO_3H \end{array}$$

Isethionic acid



$$\begin{array}{l} CH_2 . O . SO_3H \\ | \\ CH_2 . SO_3H \end{array}$$

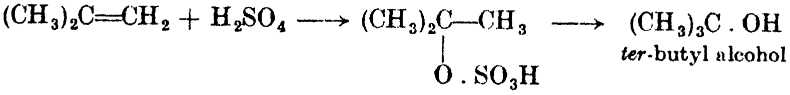
Ethionic acid



$$\begin{array}{l} CH_2 . SO_2 . O \\ | \qquad\quad | \\ CH_2 . O —SO_2 \end{array}$$

Carbyl sulphate

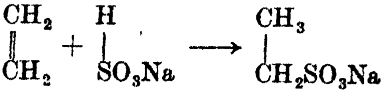
These reactions are shown by other olefines, but ethylene alone gives a primary alcohol from its acid sulphate, since in all other instances the acid residue adds on to the carbon carrying least hydrogen ; thus, with *iso*-butylene :



$$(CH_3)_2C{=}CH_2 + H_2SO_4 \longrightarrow \begin{array}{c} (CH_3)_2C—CH_3 \\ | \\ O . SO_3H \end{array} \longrightarrow (CH_3)_3C . OH$$

ter-butyl alcohol

In addition, olefines react with both sulphur dioxide and sulphates under suitable conditions, yielding not esters but stable sulphonic acids. Thus, ethylene with sodium hydrogen sulphite yields the sodium salt of ethane sulphonic acid



$$\begin{array}{c} CH_2 \\ \| \\ CH_2 \end{array} + \begin{array}{c} H \\ | \\ SO_3Na \end{array} \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_2SO_3Na \end{array}$$

*Cyclo*hexene yields *cyclo*hexane sulphonic acid.

Reduction of Olefines.—Olefines react readily with hydrogen in the presence of catalysts, even at temperatures as low as 100°. The saturated hydrocarbon is the main product. Discovered by Sabatier and Senderens in 1905,[1] this is the original reaction on which the whole science of catalytic hydrogenation is based. The original catalyst of Sabatier was nickel, but a variety of activated copper catalysts can also be used. The reaction is general, and even the high olefines can be saturated by its use. Raney nickel, or palladium will catalyse the hydrogenation of gaseous olefines at ordinary temperatures and pressures; some hindrance[1] is, however, observed with substances such as *s*-diphenylethylene.

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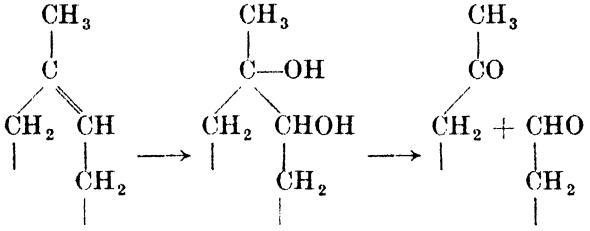
[1] P. Sabatier " La catalyse en chimie organique ", Paris, 1913.

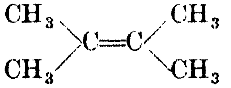
The Oxidation of Olefines.—The classical example of oxidation in this field is the decolorising of cold alkaline permanganate as a distinguishing test for olefines (Baeyer's reaction). Under controlled conditions, the glycol can be obtained :—

$$CH_2{=}CH_2 \longrightarrow CH_2OH\,.\,CH_2OH$$
$$(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2C(OH)\,.\,CH_2OH$$

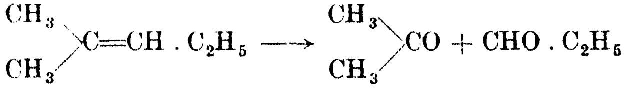
but there is a strong tendency to proceed further and to split the molecule, e.g.



a reaction which has proved valuable in terpene chemistry (q.v.). On the other hand, it must be noted that not all olefine double-bonds react with permanganate; it appears that at least one hydrogen atom must be carried by the carbons of the double bond for reaction to take place. Thus, 2, 3-dimethylbutene-2 (13) is unaffected by permanganate, whilst 2-methylpentene-2 (14) is oxidised to acetone and propanal.



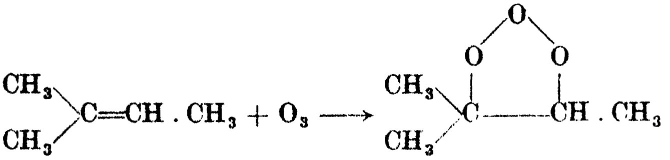
(13)



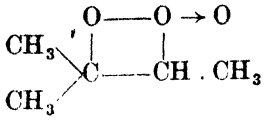
(14)

Cleavage of substituted olefines unaffected by permanganate can often be accomplished by chromic acid mixtures; although these are usually too destructive for the conversion of simpler unsaturated compounds to glycols. The use of ozone (see Appendix II for literature) as an oxidising agent leads to very interesting reactions, the net result of which is the cleavage of the unsaturated compound into two aldehydes if the —CH=CH— group is present, two ketones in the case of $\rangle C{=}C\langle$ and in the case of $\rangle C{=}CH$— one molecule each of aldehyde and ketone. The method is valuable for determining both nature and position of double bonds.

The progress of the reaction is somewhat obscure. The formation of a crystalline ozonide, often of explosive nature, is undisputed; the structure of such bodies is, however, not clear; using 2-methylbutene-2 (15) as an example, it was customary, some years ago, to write the formula of the ozonide as (16);



(15) (16)



(17)

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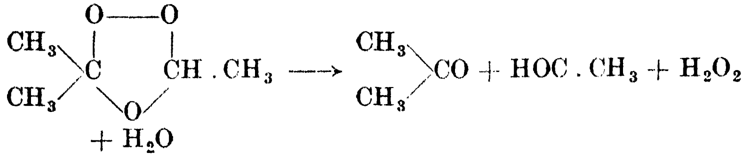
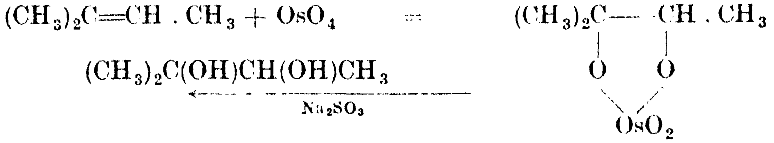
[1] Waldeland, Zartman and Adkins, *J.A.C.S.*, 1933, **55**, 4234.



(18)

this has been abandoned, having regard to the structure of ozone, for the structure (17). The older structure was proposed by Harries,[1] but Staudinger [2] has advanced the structure (18) in which the carbon atoms of the unsaturated group have been divorced. On the other hand, Briner and others [3] have examined the Raman spectra of ozonides, and report that this evidence indicates that the carbons of the double bond remain linked.

Some light is thrown on the problem by the action of osmium tetroxide which adds on to ethylenic compounds to give addition products (19), thus :—



(19)

these are quite definite in character, and can be reduced by sulphite to the glycol, thus indicating that the carbons of the original unsaturated group remain linked. Also, ethylene can add to the iron, platinum and iridium complexes to form compounds of the type $[Pt(C_2H_4)Cl_3]R$ and $[Ir(C_2H_4)Cl_3]R$.

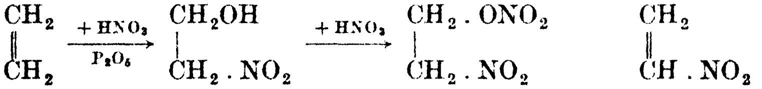
Formation of Acids from Olefines.—When ethylene is passed into caustic alkali solution in an autoclave at 50 atmospheres, and at 400°, sodium acetate and hydrogen are produced in good yield ;

$$C_2H_4 + NaOH + H_2O \longrightarrow CH_3 . COONa + 2H_2$$

propionic acid salts can be produced in the same way, but the reaction fails with higher members owing to polymerisation. Acrylic acid can be produced from ethylene and carbon dioxide at high temperatures and pressures and in the presence of catalysts :—

$$C_2H_4 + CO_2 = CH_2{=}CH . COOH$$

Nitro and Nitroso Compounds.—Olefines can be nitrated ; the reaction was studied by Wieland,[4] whose conclusion was that nitric acid adds on to ethylene

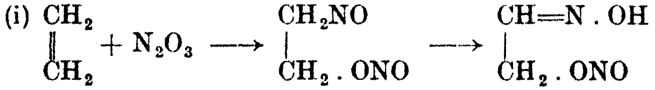


$$\begin{matrix}CH_2\\ \|\\ CH_2\end{matrix} \xrightarrow[P_2O_5]{+HNO_3} \begin{matrix}CH_2OH\\ |\\ CH_2 . NO_2\end{matrix} \xrightarrow{+HNO_3} \begin{matrix}CH_2 . ONO_2\\ |\\ CH_2 . NO_2\end{matrix} \qquad \begin{matrix}CH_2\\ \|\\ CH . NO_2\end{matrix}$$

(20) (21) (22)

to give (20), nitroethanol, which is immediately esterified to β-nitroethylnitrate (21). Nitroethanol, prepared by an alternative method, is readily esterified to the nitrate, and on treatment with phosphorus pentoxide gives nitroethylene (22). This work was studied in connection with the nitration of aromatic hydrocarbons (q.v.).

The reactions with nitrogen trioxide, nitrogen tetroxide, and with nitrosyl chloride follow the same process :—



$$\text{(i)}\ \begin{matrix}CH_2\\ \|\\ CH_2\end{matrix} + N_2O_3 \longrightarrow \begin{matrix}CH_2NO\\ |\\ CH_2 . ONO\end{matrix} \longrightarrow \begin{matrix}CH{=}N . OH\\ |\\ CH_2 . ONO\end{matrix}$$

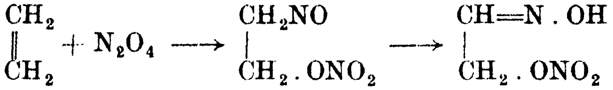
---

[1] Harries, *Ann.*, 1910, **374,** 288.

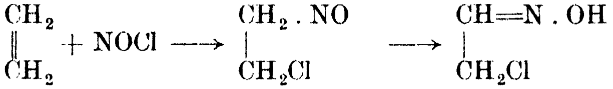
[2] Staudinger, *Ber.*, 1925, **58,** 1088.

[3] Briner, Perottet, Paillard and Susz, *Helv. Chim. Acta*, 1936, **19,** 1163.

[4] Wieland and Sakellarios, *Ber.*, **52,** 898 ; *ibid.*, 1920, **53,** 201.

(ii)


$$\begin{array}{l}CH_2\\ \| \\ CH_2\end{array} + N_2O_4 \longrightarrow \begin{array}{l}CH_2NO\\ | \\ CH_2 . ONO_2\end{array} \longrightarrow \begin{array}{l}CH{=}N . OH\\ | \\ CH_2 . ONO_2\end{array}$$

(iii)


$$\begin{array}{l}CH_2\\ \| \\ CH_2\end{array} + NOCl \longrightarrow \begin{array}{l}CH_2 . NO\\ | \\ CH_2Cl\end{array} \longrightarrow \begin{array}{l}CH{=}N . OH\\ | \\ CH_2Cl\end{array}$$

The monomeric forms of these nitrosites, nitrosates and nitrosochlorides are blue or green, but can change readily to the colourless dimeric form, or in cases where the carbon carrying the nitroso group also carries a hydrogen atom prototropic change to the colourless oxime form ensues.

Polymerisation of Alkenes.—Olefines are capable of polymerisation (23), either as in the case of ethylene, into simple substances, e.g., 1-butene, 1-hexene,

$$CH_2{=}CH_2 \xrightarrow{C_2H_4} CH_2{=}CH . CH_2 . CH_3 \xrightarrow{C_2H_4} \underset{(23)}{CH_2{=}CH . (CH_2)_3 . CH_3} \xrightarrow{C_2H_4} \underset{(24)}{CH_2{=}CH(CH_2)_5 . CH_3}$$

and 1-octene (23 and 24), or into complex substances of high molecular weight as in the case of isoprene, styrene and indene. (For mechanism of addition, see Chap. VI, Vol. III.)

The polymerisation products from the thermal treatment of ethylene and propylene, either alone or in the presence of contact catalysts such as floridin (a complex aluminosilicate of high surface), are complex, such an operation virtually becoming petroleum reconstitution (see also Appendix I). Under the circumstances of such polymerisation, cyclisation of the polymers occurs.[1] Further polymerisation leads to colourless elastic plastics of the polythene (' Alkathene ') class, which are entirely impervious to water.

Polymerisation of olefines by sulphuric acid of various strengths is an important industrial synthetic process; thus, when *iso*-butene (2-methylpropene) is absorbed in 65 per cent. sulphuric acid and the solution is heated to 100° dimerisation of the nascent *iso*-butene occurs (see p. 79). This was an early method of making *iso*-octane industrially as an aviation fuel. It was later found that addition of *iso*-butene to *iso*-butane could take place,

$$(CH_3)_2 . C{=}CH_2 + (CH_3)_3CH \longrightarrow (CH_3)_3C . CH_2 . CH(CH_3)_2$$

thus producing *iso*-octane in one operation. It is this reaction which has brought the use of *iso*-octane as an aviation fuel within the reach of possibility.

Ethylene, polymerised in the presence of ethane and *iso*-butene, gives both high boiling paraffins and olefines, which may be used for lubricating purposes.

In general, the polymerisation of butene is more easily accomplished than that of either propylene or ethylene. The polymerisation of *iso*-butene is particularly interesting, and gives rise to hydrocarbons containing up to 10 butene units. Whitmore isolated the following hydrocarbons from polymerised *iso*-butene :—

2, 4, 4-Trimethylpentene-1	$CH_2{=}C(CH_3) . CH_2 . C(CH_3)_3$
2, 4, 4-Trimethylpentene-2	$(CH_3)_2 . C{=}CH . C(CH_3)_3$
2, 2, 4, 6, 6-Pentamethylheptene-3	$(CH_3)_3 . C . CH{=}C(CH_3)CH_2 . C(CH_3)_3$
2^2, 2^2, 4, 4-Tetramethyl-2-propyl-pentene-1	$(CH_3)_3 . C . CH_2 . C(: CH_2) . CH_2 . C(CH_3)_3$
2, 4, 4, 6, 6-Pentamethylheptene-1	$CH_2{=}C(CH_3)CH_2C(CH_3)_2 . CH_2 . C(CH_3)_3$
2, 4, 4, 6, 6-Pentamethylheptene-2	$(CH_3)_2 . C{=}CH . C(CH_3)_2 . CH_2 . C(CH_3)_3$

---

[1] Ipatiev, *Ber.*, 1911, **44**, 2978.

Naturally, other products will be present in proportions too small for accurate separation and identification. As we travel up the series so the complexity of polymeric products increases ; thus pentene-1 and pentene-2 give mixtures from which have been isolated :—

2, 2, 3, 4-Tetramethylhexene-4 $(CH_3)_3C\,.\,CH(CH_3)C(CH_3){=}CH_2\,.\,CH_3$
2, 3, 4, 4-Tetramethylhexene-2 $(CH_3)_2C{=}C(CH_3)\,.\,C(CH_3)_2\,.\,CH_2\,.\,CH_3$

Addition of Sulphur Chloride to Ethylene.—When ethylene is passed into sulphur chloride, " mustard gas " 2, 2′dichlordiethylthioether $(ClCH_2\,.\,CH_2)_2S$ and sulphur are obtained. No satisfactory use has been devised for this compound, first discovered in 1860 by Guthrie, but it has been prepared in bulk for offensive purposes. Similar, but not identical, reactions are observed between selenium chloride and ethylene.

Olefine Condensations in the Presence of Catalysts.—In the presence of anhydrous aluminium chloride (ferric and stannic chlorides also serve) ethylene and its homologues react readily with aromatic hydrocarbons, to form alkyl derivatives. With benzene and ethylene, ethylbenzene is the first product, but it is not possible to obtain much more than 30 per cent. of this substance, as the reaction proceeds further to give higher derivatives. The various proportions of higher alkylated benzenes obtained depends on the amount of ethylene used and the rates of reaction of the various intermediates. From data obtained by Reid and his co-workers,[1] and by Stanley,[2] the optimum conditions for the formation of various substitution products are as follows :—

TABLE X

Product required	Moles of ethylene absorbed at 70°	Products obtained	Benzene unchanged
Mono- and di-ethylbenzenes	1·14	Monoethylbenzene, 35 per cent. Diethylbenzene (chiefly meta), 21 per cent.	32 per cent.
Triethylbenzenes	3·66	Diethylbenzenes, 10 per cent. Triethylbenzenes, 56 per cent. (mainly the 1, 2, 4-isomer) Tetraethylbenzene, 12 per cent. Hexaethylbenzene, 19 per cent.	—
Tetraethylbenzene	5·24	Triethylbenzene, 7 per cent. Tetraethylbenzene, 19 per cent. (mainly the 1, 2, 4, 5 isomer) Pentaethylbenzene, 2 per cent. Hexaethylbenzene, 72 per cent.	—
Hexaethylbenzene	5·74	Tetraethylbenzene, 9·5 per cent. Hexaethylbenzene, 91 per cent.	—

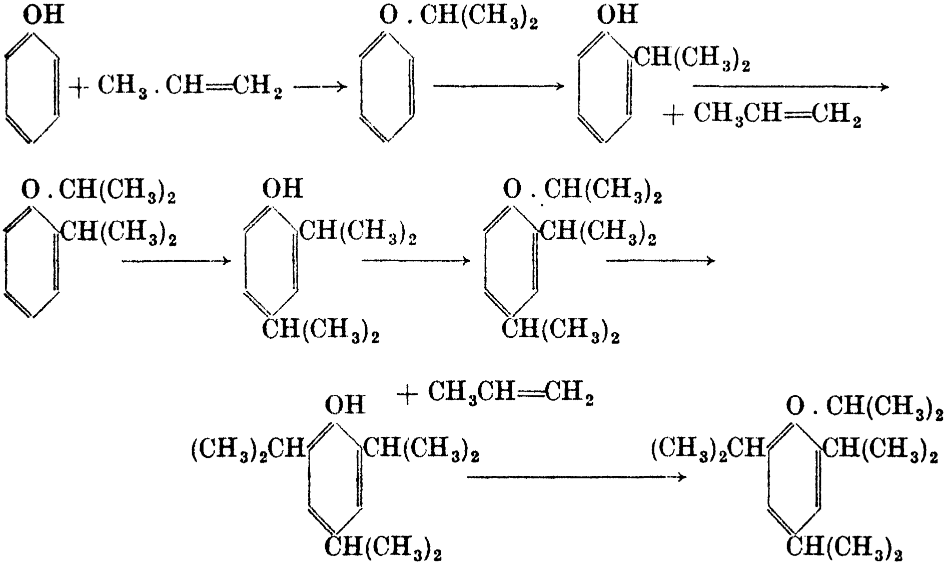
It will be observed that there is a strong tendency to form the hexaethyl derivative ; practically no pentaethyl derivative can be isolated, and only comparatively low yields of tetraethylbenzene. Somewhat different results were obtained with propylene, the absorption being slower and the tendency towards the formation of higher derivatives appeared to be hindered by the *iso*-propyl groups. It should be noted that the 2-hydrogen of propylene is the reactive one and the 2-carbon becomes attached to the aryl nucleus. Thus, a 52 per cent. yield of mono-*iso*propylbenzene is obtained by the absorption of 0·75 moles of propylene by benzene at 70° in the presence of aluminium chloride. Under similar conditions a mixture of 47 per cent. of di-*iso*propylbenzene (chiefly the meta-) and 47 per cent. of tri-*iso*propylbenzene, can be obtained by absorption of 1·93 moles; 1·97 moles of propylene gave an 88 per cent. yield of tri-isopropylbenzene (chiefly the 1, 2, 4-isomer), in all cases the product appeared to contain some 1, 2, 4, 5-tetra-isopropylbenzene (a crystalline solid, m. 117°). The reaction is general, and may be extended to higher olefines and *cyclo* olefines (e.g., *cyclo*hexene), whilst substituted benzenes, and naphthalene may serve as the substrate. A number of such substances are available industrially.

---

[1] Milligan and Reid, *J.A.C.S.*, 1922, **44**, 206 ; *Ind. Eng. Chem.*, 1923, **15**, 1048 ; Berry and Reid, *J.A.C.S.*, 1927, **49**, 3142.

[2] Stanley, *J.S.C.I.*, 1930, **49**, 349T.

The condensation of olefines with phenols in the presence of condensing agents constitutes a very important extension of the above reaction. The progress of the reaction can be best illustrated by the diagram below, constructed from the results of Sowa, Hinton and Nieuwland,[1] who used propylene and phenol in the presence of boron trifluoride. The progress of the reaction appears to be :—



In this way mono-, di- and tri-alkyl substituted phenols can be obtained. The method has proved very valuable for obtaining industrial supplies of alkyl phenols as raw materials for antiseptics (e.g., amyl cresols), thymol, oil-soluble synthetic resins (q.v.). The reaction observed with phenols, extends also to bases, so that olefines heated with arylamines under pressure yield the *p*-alkyl derivatives, e.g.,

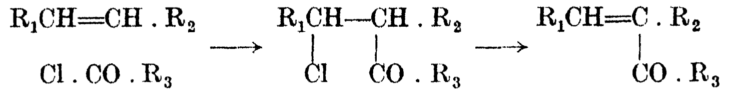
aniline + propylene ⟶ p-*iso*propylaniline
aniline + trimethylethylene ⟶ p-*ter*butylaniline, etc.

The formation of these bodies in the presence of cobalt chloride or bromide as a condensing agent gives an additional method of preparing them.[2] Acetonitrile results in very substantial yield from ethylene and ammonia, diluted with hydrogen, when passed over suitable catalysts at 450° C.,[3] and this is now the usual industrial method for its manufacture.

---

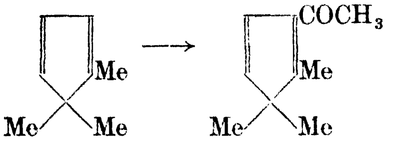
[1] Sowa, Hinton and Nieuwland, *J.A.C.S.*, 1932, **54**, 3694.
[2] Hickinbottom, *J.C.S.*, 1932, 2396; 1932, 2646.
[3] B.P. 283,163, *Brit. Chem. Abs. B.*, 1929, 275.

A further example of the additive power of the unsaturated group in olefines lies in their reaction with acid chlorides, by which unsaturated ketones can be built up, thus :—

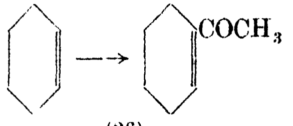


$$\begin{array}{c}R_1CH{=}CH\,.\,R_2\\ \\ Cl\,.\,CO\,.\,R_3\end{array}\longrightarrow\begin{array}{ll}R_1CH{-}&CH\,.\,R_2\\ \ \ \ \ \ | & |\\ \ \ \ \ Cl & CO\,.\,R_3\end{array}\longrightarrow\begin{array}{ll}R_1CH{=}&C\,.\,R_2\\ & |\\ & CO\,.\,R_3\end{array}$$

This reaction affords a valuable means of preparing otherwise inaccessible structures, e.g., aceto-*iso*laurolene (25) [1] and *cyclo*hexenylmethylketone (26) [2] :—



(25)



(26)

The Dienes and Higher Olefines.—There are three classes of dienes commonly met with :—

(1) The allenes, in which the twinned double bond structure

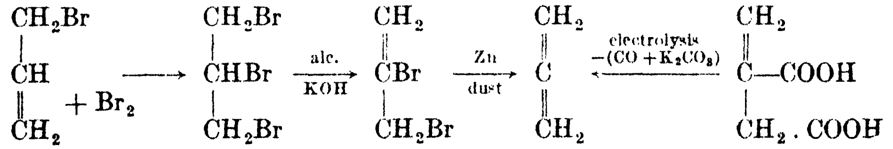
$$R_1R_2C{=}C{=}CR_3R_4$$

is characteristic (" cumulative " double-bonds).

(2) The conjugated dienes, which contain the group $R_1R_2C{=}CH.CH{=}C\,R_1R_2$

(3) Those dienes in which the two ethylene links are independent (" isolated " double-bonds).

Allene (propadiene) itself, may be prepared by the following sequence of reactions from allyl bromide :—

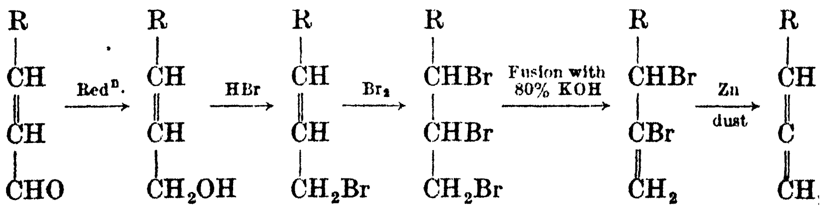


$$\begin{array}{l}CH_2Br\\ |\\ CH\\ \|\\ CH_2\end{array}+Br_2\longrightarrow\begin{array}{l}CH_2Br\\ |\\ CHBr\\ |\\ CH_2Br\end{array}\xrightarrow[\text{KOH}]{\text{alc.}}\begin{array}{l}CH_2\\ \|\\ CBr\\ |\\ CH_2Br\end{array}\xrightarrow[\text{dust}]{\text{Zn}}\begin{array}{l}CH_2\\ \|\\ C\\ \|\\ CH_2\end{array}\xleftarrow[-(CO+K_2CO_3)]{\text{electrolysis}}\begin{array}{l}CH_2\\ \|\\ C{-}COOH\\ |\\ CH_2\,.\,COOH\end{array}$$

(27) (28)

The reactions are self-explanatory, and the allene produced (27) is a gas, m.p. − 146°, b.p. − 32°. It may also be produced by the electrolysis of potassium solutions of the salt of itaconic acid (28).

Homologous allenes are mostly prepared by the method of Bouis,[3] which is sufficiently indicated by the following formulæ :—



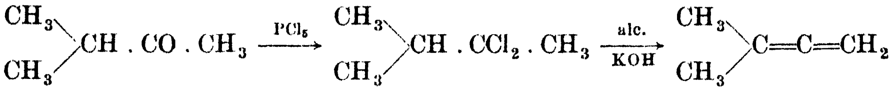
$$\begin{array}{l}R\\ |\\ CH\\ \|\\ CH\\ |\\ CHO\end{array}\xrightarrow{\text{Red}^{n}.}\begin{array}{l}R\\ |\\ CH\\ \|\\ CH\\ |\\ CH_2OH\end{array}\xrightarrow{\text{HBr}}\begin{array}{l}R\\ |\\ CH\\ \|\\ CH\\ |\\ CH_2Br\end{array}\xrightarrow{\text{Br}_2}\begin{array}{l}R\\ |\\ CHBr\\ |\\ CHBr\\ |\\ CH_2Br\end{array}\xrightarrow{\text{Fusion with 80\% KOH}}\begin{array}{l}R\\ |\\ CHBr\\ |\\ CBr\\ \|\\ CH_2\end{array}\xrightarrow[\text{dust}]{\text{Zn}}\begin{array}{l}R\\ |\\ CH\\ \|\\ C\\ \|\\ CH\end{array}$$

(29)

Thus, if $R{=}CH_3$, the starting point is crotonaldehyde and the product, methyl allene (29). Allenes can also be obtained from ketones of the series *iso*-propyl methyl ketone, thus :—

---

[1] Blanc, *Bull. Soc. Chim.*, 1899 (3), **19**, 699.
[2] Darzens, *C.R.*, 1910, **150**, 707.
[3] Bouis, *ibid.*, 1926, **182**, 788 ; **183**, 133.



The boiling points of the chief allenes are given in the table below, where R is taken relative to formula (29) :—

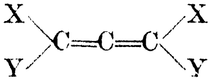
TABLE XI

The Allenes

R =	B.Pt.
H *	− 32°
CH_3	+ 19°
C_2H_5	45°
n-C_3H_7	78°
i-C_3H_7	70°
n-C_4H_9	106°
i-C_4H_9	96°
$(CH_3)_2C{=}C{=}C(CH_3)_2$	70°

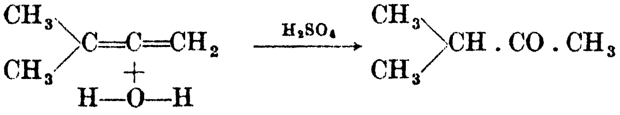
* m.p. = − 146°.

Many complex allenes have been prepared to test the theories of stereochemistry (see Vol. III), since substances of the structure

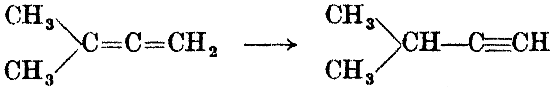


should be capable of existing in optically active forms. They were first obtained by Mills and Maitland [1] in 1935, and almost simultaneously by Kohler, Walker and Tishler.[2]

The reactions of allenes are interesting in relation to the theories dealing with unsaturation. Allene itself adds on two atoms of bromine at 0° to give 2, 3-dibrompropene, which will take up a further pair of bromine atoms to give 1, 2, 2, 3-tetrabrompropane, a substance m.p. 11° C., b.p. 116°/9 mm. With sulphuric acid and water a methyl ketone is obtained by addition of the elements of water :—



One valuable reaction of the allenes is their conversion to acetylenes on boiling with sodium in an inert solvent [3]



(30) (31)

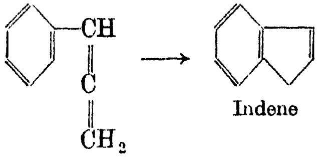
thus dimethylallene (30) yields 3-methylbutyne-1 (31) ; the sodium derivative is actually obtained, but can be converted to the hydrocarbon by dilute acid, or used in carrying out Moureu's reaction (see p. 113). The aryl substituted allenes,[1] unable to rearrange to an acetylene, form indene derivatives, thus

---

[1] Mills and Maitland, *J.C.S.*, 1936, 987 (a note was published in *Nature*, 1935, **135**, 994, announcing this discovery).

[2] Kohler, Walker and Tishler, *J.A.C.S.*, 1935, **57**, 1743.

[3] Favorsky, *J. Pr. Chem.*, 1888, 2, **37**, 417 ; 1891, 2, **44**, 208.



Indene

Conjugated Diolefines.—The commonest conjugated diolefines are shown, with their characterisation compound with maleic anhydride, in the following table :—

TABLE XII

Diene	Formula	B.P.	Tetrahydrophthalic anhydride derivative	
Butadiene-1, 3	$CH_2=CH\ .\ CH=CH_2$	1°		m. 104°
2-Methylbutadiene (Isoprene)	$CH_2=C(CH_3)CH=CH_2$	37°	4-Methyl-	m. 64°
Pentadiene-1, 3 (Piperylene)	$CH_2=CH\ .\ CH=CH\ .\ CH_3$	43°	3-Methyl-	m. 62°
2-Methylpentadiene-1, 3	$CH_2=C(CH_3)CH=CH\ .\ CH_3$		3, 5-Dimethyl-	m. 57°
3-Methylpentadiene-1, 3	$CH_2=CH\ .\ C(CH_3)=CH\ .\ CH_3$		3, 4-Dimethyl-	m. 67°
Hexadiene-2, 4	$CH\ .\ CH=CH\ .\ CH=CH\ .\ CH$	81°	3, 6-Dimethyl-	m. 96°
2, 3-Dimethylbutadiene-1, 3	$CH_2=C(CH_3)\ .\ C(CH_3)=CH_2$	70°	4, 5-Dimethyl-	m. 79°
2, 3-Dimethylpentadiene-1, 3	$CH_2=C(CH_3)C(CH_3)=CH\ CH$		3, 4, 5-Trimethy	m. 49°
cyclo-Pentadiene	$CH=CH\ CH=CH\ .\ CH$	41°	—	m. 165°
cyclo-Hexadiene-1, 3	$CH=CH\ .\ CH=CH\ .\ CH_2\ .\ CH_2$		—	m. 147°

Butadiene.—The pyrolysis of many organic compounds gives some butadiene. Although a constant ingredient of cracked gases of various types, butadiene $CH_2=CH\ .\ CH=CH_2$, is an extremely difficult substance to obtain in small quantities for experimental work. The best source in this country for small quantities is the so-called " railway hydrocarbon " (obtained by the " cracking " of shale-oil to prepare illuminating gas for railway carriages ; the oil is a by-product) or the " first condensate " from the vapour phase cracking of crude petroleum for bitumen. Either of these liquids contains a large amount of dissolved butadiene, and when heated over a tiny flame the butadiene is evolved, and may be passed through bromine in ice to obtain the butadiene tetrabromide. Pure butadiene can be obtained from this product by boiling it with an alcoholic suspension of zinc dust. For the preparation of larger quantities the best starting point is butylene glycol (butandiol-1, 3). If a mixture of steam and butandiol-1, 3 vapour is passed over a dehydration catalyst at 270° C., a yield of up to 90 per cent. of butadiene can be obtained. This is actually a simplified form of Ostromislenski's [2] double catalytic process for preparing butadiene, in which a mixture of ethanol and ethanal was passed first over a copper catalyst and then over heated alumina. It is assumed that aldol and butylene glycol are produced under the influence of the copper catalyst, and that the glycol is dehydrated to butadiene.

Harries [3] obtained butadiene for experimental purposes by dropping 2, 3-dibrombutane into red-hot soda lime :—

$$CH_3\ .\ CHBr\ .\ CHBr\ .\ CH_3 \longrightarrow CH_2=CH\ .\ CH=CH + 2HBr$$

---

[1] Vorlander and Siebert, *Ber.*, 1906, **39**, 1030.

[2] Ostromislenski and Kelbasinski, *J. Russ. Phys.-Chem. Soc.*, 1915, **47**, 1509.

[3] Harries, *Ann.*, 1911, **383**, 176, 181.

The product is contaminated by other substances, and can only be satisfactorily utilised by conversion to the tetrabromide and regeneration by zinc and alcohol.[1] Many variations of this method have been described :—

TABLE XIII

1, 2, 3-Tribrombutane	Jacobson [2]	Pass vapour through tube furnace packed with soda-lime at 530–550°
Dichlorbutane	Perkin,[3] Muskat and Northrup[4]	Mixed dichlorbutanes passed over soda-lime at 700–730°
1-Chlorbutene-2 (Crotyl chloride)	Jacobson	Ditto

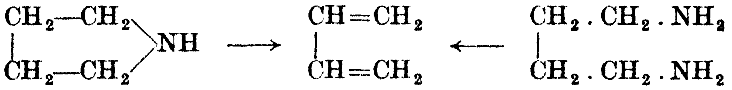
Lebedev,[5] claimed a 30 per cent. conversion of ethanol to butadiene by passage over heated alumina and zinc oxide at 400°, and 190 mm. pressure. The method appears not to have been developed.

A plant has recently been erected in the United States of America to produce 15,000 tons annually of butadiene. Butane from natural or cracker gas is the raw material, and is heated at low pressure to 565°, when part of the butane is cracked to butene and hydrogen, and part to butadiene :—

$$C_4H_{10} \longrightarrow C_4H_8 + H_2 \longrightarrow C_4H_6 + 2H_2$$

The mixture of gases is separated into two fractions, a butane-butene fraction, which is passed to a second reactor, and a butadiene fraction. The gas from the second reactor is mixed with the butadiene fraction from the first reactor and the butadiene (approx. 17 per cent.) removed by compression to 115 lb. per sq. in., the liquid butadiene being withdrawn. The approximate cost on the scale adopted is 3d.–4d. per gallon.

Other methods of obtaining butadiene which are constitutionally, but not economically, interesting are the exhaustive methylation (q.v.) of pyrrolidine and 1, 4-diaminobutane :—



Butadiene is a gas at ordinary temperatures, condensing to a colourless mobile liquid. It has a powerful and unpleasant smell.

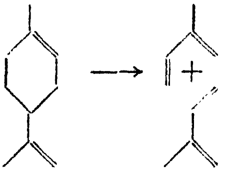
Isoprene.—The production of isoprene by the distillation of rubber drew attention to the relation between the two substances and the casual observation that the reverse action can take place led to the discovery of ' synthetic ' rubber. Much attention was focussed on this hydrocarbon because of its potentialities in relation to elastopolymers (see Appendix II), and numerous methods are available for its production. These may be classified as

(1) Pyrolytic methods.
(2) Constitutional syntheses of theoretical interest only.
(3) Synthetic methods for industrial production.

Of the first class, the passage of limonene, dipentene (32) or turpentine vapour over a heated platinum grid at low pressure yields a very high proportion of isoprene (33) :—

---

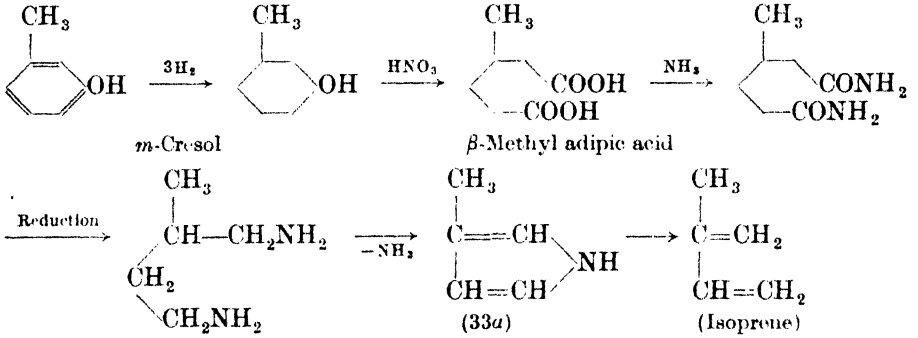
[1] Thiele, *Ann.*, 1899, **308**, 333. (See also Birch, *Ind. Eng. Chem.*, 1928, **20**, 474.)
[2] Jacobson, *J.A.C.S.*, 1932, **54**, 1545. [3] Perkin, *J.S.C.I.*, 1912, **31**, 616.
[4] Muskat and Northrup, *J.A.C.S.*, 1930, **52**, 4050.
[5] Lebedev, B.P. 1929, 331, 482.



(32) (33)

whilst this is, apparently, a method that might become suitable for large scale production it must be remembered that the production of turpentine is limited.

Examples of the second class are the exhaustive methylation of 3-methylpyrrolidine (33*a*) (2-methyl-1, 4-epaminobutane) which gives isoprene, and the analogous reaction with 1, 4-diamino-2-methylbutane, which goes back to *m*-cresol as a starting point, thus :—



The decomposition of pure 2, 4-dichloro-2-methylbutane by alcoholic potash may also be cited as a typical example of the second class, which can be brought into the third class by substituting the crude chlorination product of *iso*-amyl chloride for the pure chloro body, and passage over soda-lime at 460–480° for the heating with alcoholic potash.

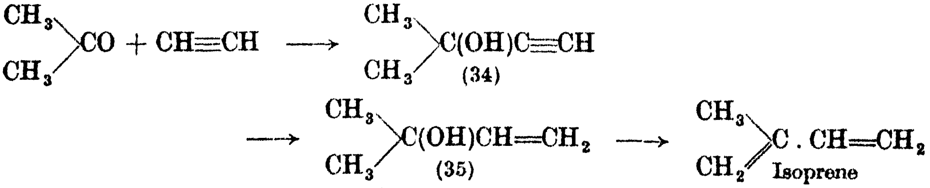
$(CH_3)_2 . CH . CH_2 . CH_2Cl \longrightarrow (CH_3)_2CCl . CH_2 . CH_2Cl$

4-Chloro-2-methylbutane (*iso*-amyl chloride) — 2, 4-Dichloro-2-methylbutane

$\longrightarrow CH_2{=}C(CH_3)CH{=}CH_2$

Isoprene

An industrially important method of obtaining isoprene is the condensation of acetone and acetylene in the presence of sodium to give 2-methyl-butyne-3-ol-2 (34). It is possible catalytically to reduce this quantitatively to the 2-methyl-butene-3-ol-2 (35) which can also be catalytically dehydrated to isoprene :—

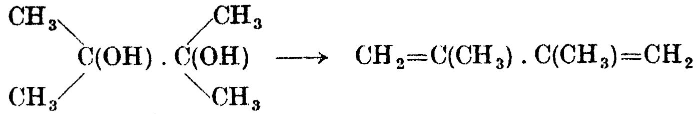


$$(CH_3)_2CO + CH{\equiv}CH \longrightarrow (CH_3)_2C(OH)C{\equiv}CH \quad (34)$$

$$\longrightarrow (CH_3)_2C(OH)CH{=}CH_2 \quad (35) \longrightarrow \begin{matrix} CH_3 \\ CH_2 \end{matrix}\!\!>\!\!C . CH{=}CH_2 \quad \text{Isoprene}$$

Isoprene is a pungent smelling liquid with physical properties very similar to those of ordinary ether.

Of the other conjugated dienes, 2, 3-dimethylbutadiene is of interest because it can be obtained from acetone in two simple stages, first by reduction and condensation of two molecules of the latter to pinacone (36), and by the catalytic dehydration of pinacone to the diene :—



$$(CH_3)_2C(OH) . C(OH)(CH_3)_2 \longrightarrow CH_2{=}C(CH_3) . C(CH_3){=}CH_2$$

(36)

Pentadiene-1, 3 (piperylene) is the only other simple, open-chain conjugated diene commonly encountered. Apart from its incidental occurrence in the exhaustive methylation of piperine, it may be obtained fairly readily from pentanol-3, by the following sequence of reactions :—[1]

$CH_3CH_2CH(OH) . CH_2CH_3$	Dehydration with 50 per cent. sulphuric acid
$CH_3CH{=}CH . CH_2CH_3$	Bromination in hexane at — 20°
$CH_3CHBr . CHBr . CH_2CH_3$	Passage over soda-lime at 500°
$CH_2{=}CH . CH{=}CH . CH_3$	↓

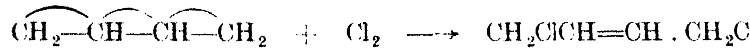
Since pentanol-3 is industrially available, this method is suitable for laboratory use.

Reactions of the Conjugated Dienes.—The conjugated dienes are phenomenally reactive ; they exhibit a very wide variety of addition reactions, of which polymerisation is merely one phase.

The addition of chlorine to butadiene has been a reaction provocative of much discussion, since four products are obtainable.

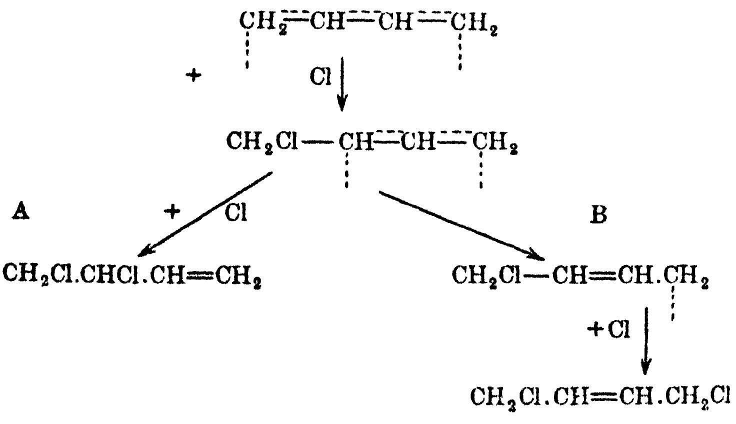
(1) $CH_2Cl . CHCl . CH{=}CH_2$	1, 2-Dichlorbutene-3
(2) $CH_2Cl . CHCl . CHCl . CH_2Cl$ (racemic and meso forms)	1, 2, 3, 4-Tetrachlorbutane
(3) $CH_2Cl . CH{=}CH . CH_2Cl$	1, 4-Dichlorbutene-2

It was the formation of substances of the latter type that led Thiele to formulate his theory of 'partial valencies', in which he sought to explain the unusual additive behaviour of conjugated double bonds. This theory is more fully discussed in a later volume, but it is necessary here to remark that whilst the Thiele conception (leading to the formulation of butadiene as



$$CH_2{-}CH{-}CH{-}CH_2 + Cl_2 \longrightarrow CH_2ClCH{=}CH . CH_2Cl$$

in which there is exhibited a residual or 'partial' valency on the 1 and 4 carbon atoms) would lead us to predict 1 : 4 addition, it does not, in itself, account for the formation of 1, 2-dichlorobutene-3 as well. There is, too, the difficulty of conceiving the mechanism of the implied simultaneous addition of the halves of a chlorine molecule in positions 1 and 4. The most probable course of such reactions is that outlined in the diagram below :—



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[1] Farmer and Warren, *J.C.S.*, 1931, 3221.

After the first chlorine addition the compound can behave in two different ways and the ratio of the quantities of the 1, 2- and 1, 4-addition products will depend on the velocities of reactions A and B respectively. There are instances where the 1, 4-addition predicted by Thiele's original hypothesis takes place only to a very limited extent, the 1, 2-addition product predominating. It is assumed in such cases that the reaction B (of the scheme above) is slow, often due to hindrance. Some addition products of hydrocarbons containing conjugated bonds is given in the table below :—

TABLE XIV

Substance	Formula	Method	Addition product	
			1, 2	1, 4
Butadiene-1, 3	$CH_2=CH.CH=CH_2$	Br added to butadiene in $CHCl_3$ at — 15°	37	63
2-Methylbutadiene-1, 3	$CH_2=C(CH_3).CH=CH_2$	„ „	20	80
2, 3-Dimethylbutadiene-1, 3	$CH_2=C(CH_3)C(CH_3)=CH_2$	Br in hexane at — 10°	35	65
2-Methylpentadiene-1, 3	$CH_2=C(CH_3)CH=CH.CH_3$	„ „	28	72
Hexadiene-2, 4	$CH_3.CH=CH.CH=CH.CH_3$	„ „	90	10
Phenylbutadiene-1, 3	$C_6H_5.CH=CH.CH=CH_2$	All conditions	100	—

It will be noted that hexadiene-2, 4 suffers 1, 2-addition very largely, indicating that reaction B (above) is slowed down by the presence of two terminal methyl groups.

The addition of halogen acids to conjugated dienes seldom gives the complete 1, 4-addition required by Thiele's original conception ; some 1, 2-addition always takes place. Meisenburg[1] claimed an 85 per cent. yield of 1, 4-addition product 1-bromobutene-2(*iso*-crotyl bromide) from butadiene and hydrogen bromide in acetic acid

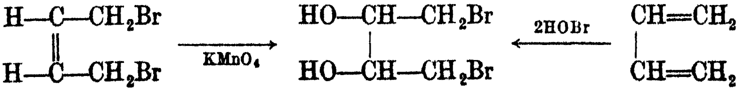
$$CH_2=CH.CH=CH_2 + HBr \longrightarrow CH_2Br.CH=CH.CH_3$$

The halogen acid addition products of isoprene are largely dependent on the conditions of reaction, and are discussed in Chapter IV.

The conjugated dienes react readily with hypochlorous acid or with hypobromites to give the corresponding halohydrins. With isoprene three compounds are isolated.[2]

(1) $CH_2Br.C(CH_3)=CH.CH_2OH$	1-Bromo-2-methylbutene-2-ol-4. A product of 1, 4-addition, present to an extent of about 50 per cent.
(2) $CH_2OH.C(CH_3)=CH.CH_2Br$	4-Bromo-2-methylbutene-2-ol-1. A product of 1, 4-addition in a reverse direction to that of (1). Present in small quantity only.
(3) $CH_2BrC(CH_3)(OH).CH=CH_2$	1-Brom-2-methylbutene-3-ol-2. A product of 1, 2-addition ; present up to 20 per cent.

Further action of hypobromous acid gives the *bis*-halohydrins, which may also be obtained and structurally characterised by the action of permanganate on the *cis*- and *trans*-dibrom addition products. Thus :—



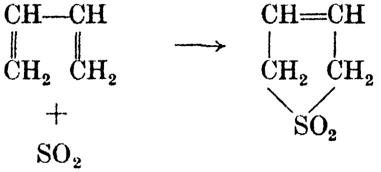
$$\begin{matrix} H—C—CH_2Br \\ \| \\ H—C—CH_2Br \end{matrix} \xrightarrow[KMnO_4]{} \begin{matrix} HO—CH—CH_2Br \\ | \\ HO—CH—CH_2Br \end{matrix} \xleftarrow{2HOBr} \begin{matrix} CH=CH_2 \\ | \\ CH=CH_2 \end{matrix}$$

---

[1] Meisenburg, U.S.P. 1,725,156 (1929).

[2] Ingold and Smith, *J.C.S.*, 1931, 2752.

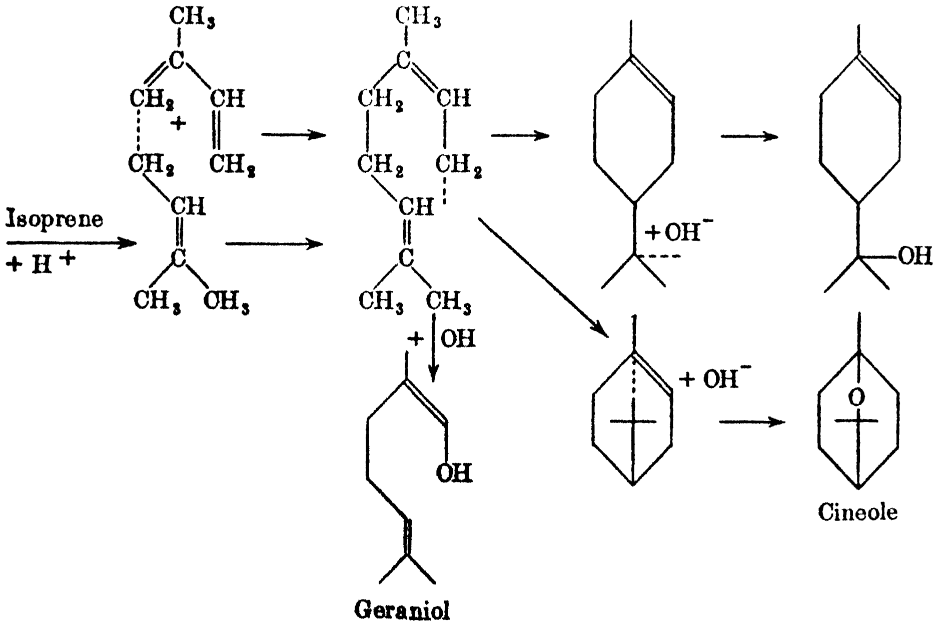
Conjugated dienes add sulphur dioxide forming cyclic sulphones and also react with sulphuric acid to give complex hydrocarbons, alcohols, etc. ; the former reaction is the basis of Edelenau's method for the removal of dienes from petroleum spirit. The combination of conjugated dienes with sulphur dioxide is a reaction of great importance. The reaction takes place readily and almost quantitatively, and serves as a basis for the analytical identification of the hydrocarbons. Chemically, the reaction takes a course which is similar to that of a Diels-Alder condensation :—



The sulphones are stable substances crystallising well from solvents, and in the case of butadiene giving very large monoclinic tablets up to several inches in size. The formation of such compounds is the basis of the treatment of automobile spirit with liquid sulphur dioxide to remove ' gum-forming ' substances. The decomposition of the sulphones at 120–130° into the hydrocarbon and sulphur dioxide serves to regenerate the former in a pure condition, and is the basis of an ' actually used ' process for recovering butadiene from cracker gas. The reaction between isoprene and sulphuric acid in acetic acid is particularly complex and yields a wide variety of products from which geraniol, geranyl acetate, terpineol, cineole, linalool and other substances may be isolated. It is not possible to give a precise account of the mechanism involved in these reactions, but many ingenious ' explanations ' have been devised. Thus, if isoprene be regarded as converted by hydrogen ions to a form :—

$$(CH_3)_2C{=}CH\,.\,CH_2$$

we could expect reactions such as :—

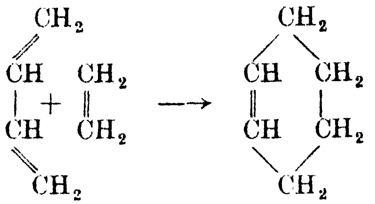


The polymerisation reactions of conjugated dienes are discussed in Appendix I.

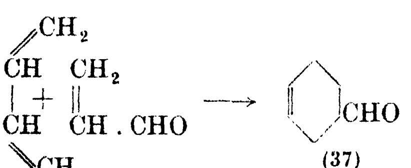
THE DIELS-ALDER SYNTHESIS

Albrecht[1] showed that a condensation reaction took place between cyclopentadiene and quinones, but he did not determine the constitution of the products; the observations of Euler and Josephson[2] showed that isoprene and benzoquinone gave a crystalline condensation product, but it remained for Diels and Alder[3] in 1928 to explore fully and to elucidate the important condensation now usually associated with their names.

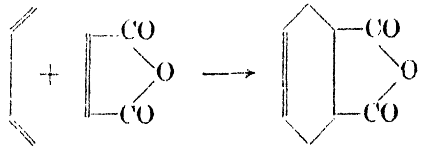
The essence of the Diels-Alder reaction is the 1, 4-addition of a diene, or enyne to an olefine or acetylene. Thus, the simplest example would be the addition of butadiene to ethylene, giving a cyclohexene, a reaction which was



shown to proceed normally by Joshel and Butz.[4] The reaction is more easy to regulate when the ethylenic compound is of the type $RCH{=}CH\,.\,CO\,.\,R''$, where the products are (using butadiene) tetrahydrobenzaldehyde (37) and tetrahydrophthalic anhydride (38) respectively:—



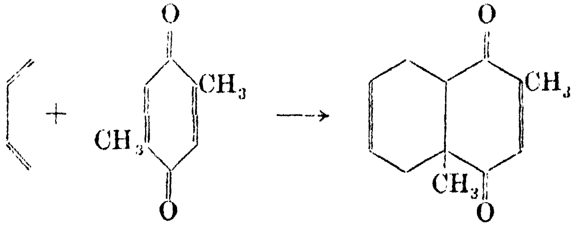
(37)
Tetrahydro-
benzaldehyde



(38)
Tetrahydro-
phthalic anhydride

The bulk of the work on this reaction has been done with maleic anhydride; some characteristic examples using other intermediates are shown below:—

1. The addition of butadiene to *p*-xyloquinone[5] giving a hydrogenated naphthoquinone carrying an angular methyl group (39):—



(39)

2. The addition of 2, 3-dimethylbutadiene[6] to 3-chloro-1, 2-naphthoquinone (40) proceeding initially to an angular chloro-phenanthrenequinone derivative (41) which readily loses hydrogen chloride to yield (42):—

---

[1] Albrecht, *Ann.*, 1906, **348**, 31.

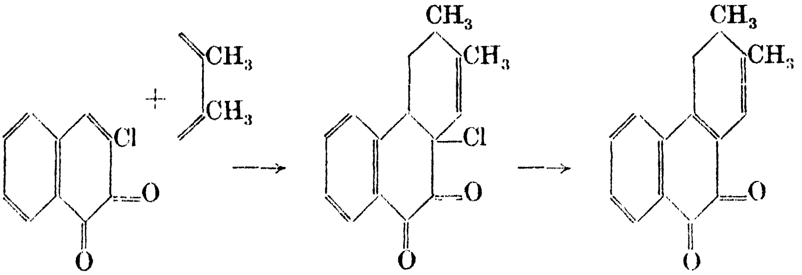
[2] Euler and Josephson, *Ber.*, 1920, 53B, 822.

[3] Diels and Alder, *Ann.*, 1928, **460**, 98.

[4] Joshel and Butz, *J.A.C.S.*, 1941, **63**, 3350.

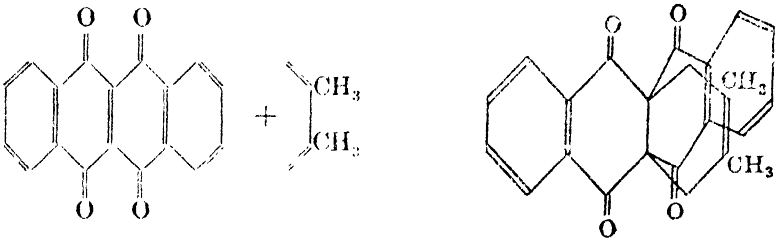
[5] Fieser and Seligman, *Ber.*, 1935, **68B**, 1747.

[6] Fieser and Dunn, *J.A.C.S.*, 1937, **59**, 1021.



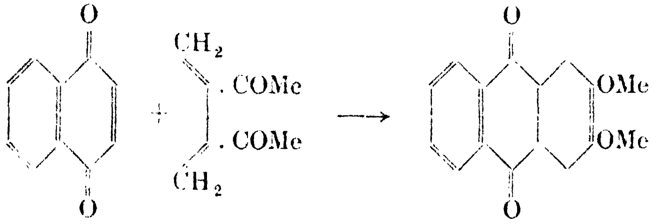
(40) (41) (42)

3. The formation of triple fused rings by addition across the central double bond, as with naphthacenediquinone (43) and 2, 3-dimethylbutadiene[1] :—



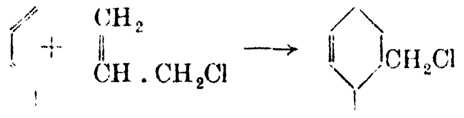
(43)

4. 2, 3-Dimethoxybutadiene and 1, 4-naphthoquinone (44) condense as shown to give an otherwise unobtainable anthraquinone (45) derivative[2] :

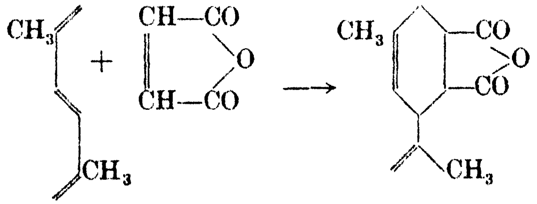


(44) (45)

5. Kharasch and Sternfeld[3] noted a Diels-Alder condensation taking place between hexatriene-1, 3, 5 and allyl chloride :—



whilst the corresponding 2, 5-dimethylhexatriene-1, 3, 5 reacts normally with maleic anhydride



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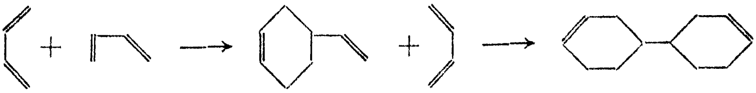
[1] Favorskaya and Zakharova, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 446.

[2] Johnson, Jobling and Bodamer, *J.A.C.S.*, 1941, **63**, 131.

[3] Kharasch and Sternfeld, *ibid.*, 1939, **61**, 2318.

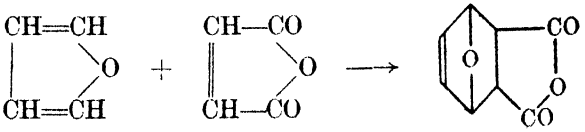
6. The dimerisation of butadiene and similar hydrocarbons proceeds largely according to a Diels-Alder condensation :—



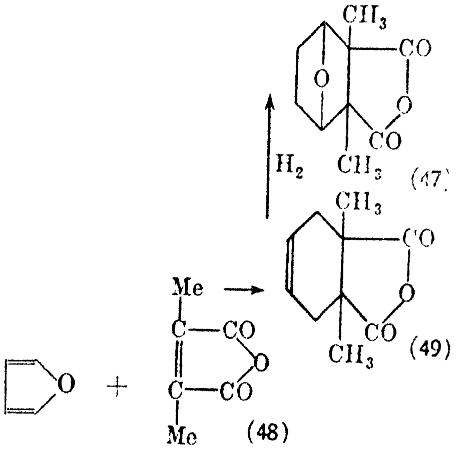
which accounts also for the presence of octahydrodiphenyl in the reaction mixture.

It will be clear from the foregoing examples that the Diels-Alder reaction of dienes is capable of the widest possible application, and will probably become one of the more important synthetic approaches to the synthesis of steroids and related compounds.

The condensation of furan and maleic anhydride proceeds readily to give tetrahydroendoxyphthalic anhydride (46),[1] which is of special interest on account of its relation to the suggested structure for cantharidin, the vesicant principle of Spanish flies. Claims made that the dimethyl compound (47) could be obtained by condensing furan and pyrocinchoninic anhydride (48) have not yet been proved by repetition of the work.[2]



(46)



(47)

(48)

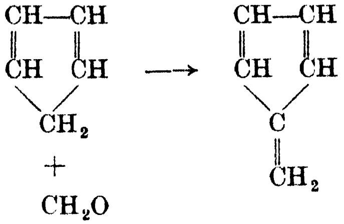
(49)

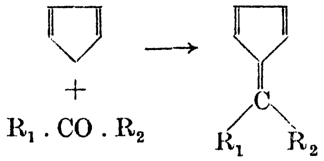
Cyclopentadiene.—One of the most reactive of conjugated dienes is cyclopentadiene, which can be isolated from the first runnings of crude coal tar benzene, from which its b.p. 41° enables it to be separated easily. It also occurs in cracked spirit and in the form of its dimer is an article of commerce. The reactivity of this diene is not confined to that of the conjugated double bond, since the methylene group is also extremely reactive. Thus, it forms a potassium derivative (cf. pyrrole) and reacts readily with aldehydes and ketones to give the fulvenes, a series of coloured hydrocarbons (see Vol. III, Colour and Constitution) :—

---

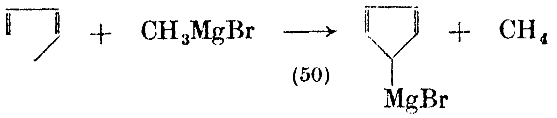
[1] Diels, Alder and Nanjoks, *Ber.*, 1929, **628**, 554.
Diels, Alder, Nieuburg and Schmalbeck, *Ann.*, 1931, **490**, 243.
Diels and Olson, *J. Pr. Chem.*, 1940, **156**, 285.

[2] Diels and Olson, *loc. cit.*



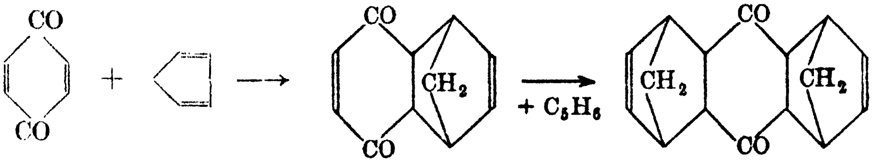


Another sign of the active methylene group in cyclopentadiene is its reaction with methyl magnesium bromide to give methane and the cyclopentadienyl Grignard compound (50) :—

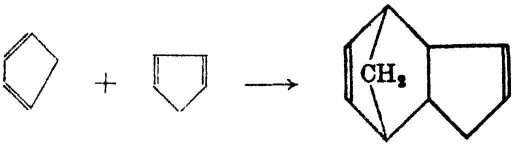


(50)

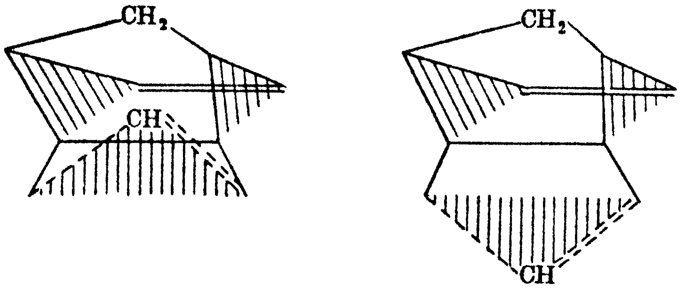
In addition, cyclopentadiene can give an extensive range of Diels-Alder condensations, in which it is particularly valuable for producing the endomethylene structure, e.g., quinone and cyclopentadiene give a single and double condensation thus :—



An analogous reaction is responsible for the dimerisation of cyclopentadiene which takes place readily at ordinary temperatures. Thus, Alder and his co-workers[1] obtained cyclopentane diacid-1, 3 from the dimer (51) by oxidation of its hydrogenated form. The dimer exists in two stereoisomeric forms ; the endomethylene group compels the six-ring to adopt the ' bed-shape ' ; the *cis*-dimer has the cyclopentene ring on the same side as the endomethylene group ; in the trans-isomer they are on opposite sides :—



(51)



cis- trans-

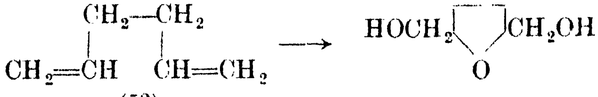
Dicyclopentadiene

---

[1] **Alder, Stein and Finzenhagen,** *Ann.*, 1931, **485**, 223.

Dienes with Isolated Double Bonds

Hexadiene-1, 5 (diallyl) is the commonest hydrocarbon containing two isolated double bonds (52). A liquid boiling at 61°, it may be obtained by the action of sodium on allyl bromide;[1] its properties are those to be expected of an unsaturated compound and the two double bonds react independently. In nearly all oxidative reactions, e.g., with peroxides, hexadiene-1, 5 is converted to tetrahydro-furan derivatives:—



(52)

In the same way methallylbromide (3-bromo-2-methylpropene-1) yields 2, 5-dimethylhexadiene-1, 5, b. 114°, which has, however, a pronounced tendency to pass into the more symmetrical structure 2, 5-dimethylhexadiene-2, 4:—

$$CH_2{=}C(CH_3)CH_2 . CH_2 . C(CH_3){=}CH_2 \longrightarrow (CH_3)_2CH{=}CH . CH{=}C(CH_3)_2$$

Trienes and Higher Olefines

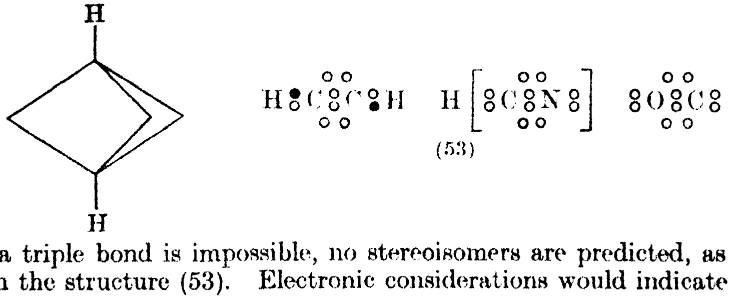
Our knowledge of the trienes is largely due to the work of Kharasch and his co-workers,[2] who prepared hexatriene-1, 3, 5 by the action of sodamide in liquid ammonia on allyl chloride:—

$$CH_2{=}CH . CH_2Cl + ClCH_2 . CH{=}CH_2 \longrightarrow CH_2{=}CH . CH{=}CH . CH{=}CH_2$$

Hexatriene-1, 3, 5 is a colourless volatile liquid, b. 77–78°, density 0·7175, which is intensely reactive.

The Acetylenes

The initial member of the series, acetylene or ethyne C_2H_2, is by far the best known, and in general, hydrocarbons containing a triple bond are rarely met with. The significance of the conventional triple bond as in $CH{\equiv}CH$ is not so much an enhanced degree of unsaturation as an altered arrangement of electrons. Thus, although the triple bond has the potentiality of increased addition as compared with the double bond, the tendency towards the formation of additive compounds is, in many cases, less than that observed with the double bond. This is in accordance with the stereochemical view that although free rotation at a triple bond is impossible, no stereoisomers are predicted, as may be seen from the structure (53). Electronic considerations would indicate that the two carbons in acetylene share their pairs of electrons, and that a comparatively stable electron configuration is produced similar to that in hydrocyanic acid and carbon monoxide. This is, to some extent, supported by the ease with which the hydrogen of acetylene is replaced by metals.



(53)

Unfortunately, the simple method for the preparation of the parent member of this series, acetylene, by the action of water on calcium carbide, cannot be extended to higher members. The acetylenes are usually prepared from the corresponding ketone, which with phosphorus pentachloride gives the dichloro-compound (54). When this compound is distilled from powdered potassium

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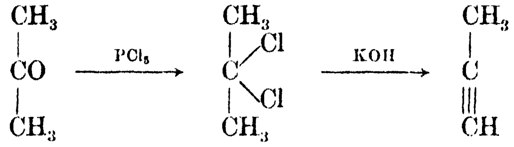
[1] Cortese, *Ber.*, 1929, **62B**, 504.

[2] Kharasch, Nudenberg and Sternfeld, *J.A.C.S.*, 1940, **62**, 2034. Kharasch and Sternfeld, *ibid.*, 1939, **61**, 2318.

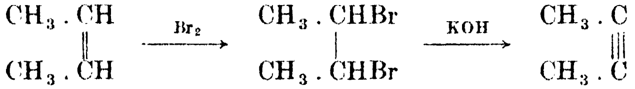


(54)

hydroxide, or is heated under reflux with an alcoholic solution of the same reagent, the corresponding acetylene is formed. Care must be taken not to overheat during the last stage as the monoethyl acetylene has a tendency to isomerise thus :—

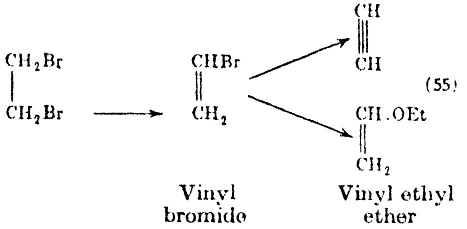
$$CH_3 \,.\, CH_2C{\equiv}CH \rightleftarrows CH_3 \,.\, C{\equiv}C \,.\, CH_3$$

the unsaturated link moving towards the centre of the molecule. A variant method is to take the corresponding olefinic compound, allow it to add bromine across the double bond and to heat the dibromo-compound with alcoholic

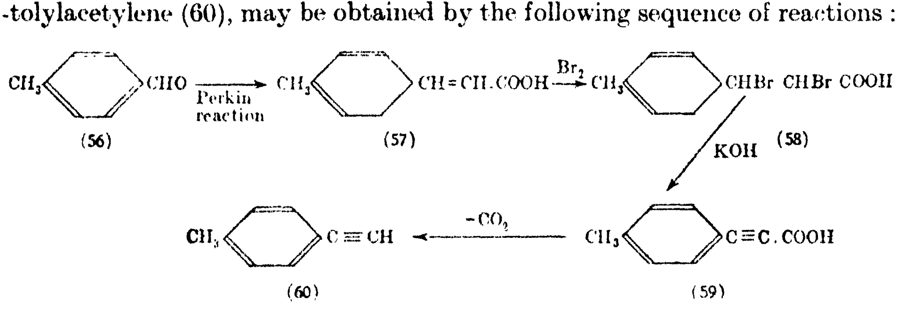


$$\begin{matrix} CH_3\,.\,CH \\ \| \\ CH_3\,.\,CH \end{matrix} \xrightarrow{Br_2} \begin{matrix} CH_3\,.\,CHBr \\ | \\ CH_3\,.\,CHBr \end{matrix} \xrightarrow{KOH} \begin{matrix} CH_3\,.\,C \\ ||| \\ CH_3\,.\,C \end{matrix}$$

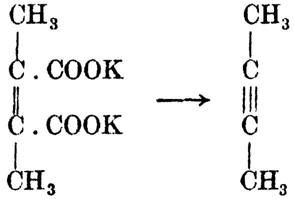
potash. Attempts to apply this reaction to the preparation of acetylene itself are not particularly successful, partly because the vinyl bromide formed as an intermediate is very volatile, and partly because it reacts readily with alcoholic potash giving vinyl ethyl ether (55) :—



Acetylenes are also readily obtained by the elimination of carbon dioxide from acids in which a triple bond is adjacent to the carboxyl group. This method is particularly adapted to the preparation of aryl substituted acetylenes, e.g., *p*-tolylacetylene (60), may be obtained by the following sequence of reactions :—



Perkin's reaction with tolualdehyde (56) sodium acetate and acetic anhydride (58) leads to 4-methyl cinnamic acid (57), this giving a dibromo compound (58) by direct addition. The latter, with alcoholic potash parts with the elements of two molecules of hydrogen bromide and forms 4-methylphenyl propiolic acid (59) which in turn gives tolylacetylene by dry distillation. Mention should also be made of Kolbe's method of preparing alkynes by electrolysing solutions of potassium salts of unsaturated acids, e.g.

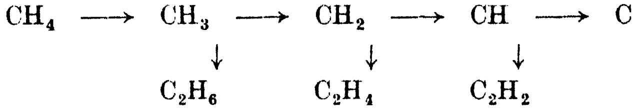


$$\begin{matrix} CH_3 \\ | \\ C.COOK \\ \| \\ C.COOK \\ | \\ CH_3 \end{matrix} \longrightarrow \begin{matrix} CH_3 \\ | \\ C \\ ||| \\ C \\ | \\ CH_3 \end{matrix}$$

Acetylene itself is a colourless gas, which, when pure, has a pleasant ethereal odour. As usually obtained from calcium carbide, its unpleasant smell is largely due to phosphine obtained from traces of calcium phosphide which are always present in commercial calcium carbide. A small amount of acetylene can be obtained by striking a carbon arc in an atmosphere of hydrogen, and it is often one of the products of incomplete combustion of hydrocarbons. The incomplete combustion of methane to give acetylene is a reaction of some importance in studies on combustion. Although the reaction may be written :—

$$2CH_4 + 3O = 3H_2O + C_2H_2$$

it is undoubtedly true that the sequence of reactions shown in the diagram below must take place, by progressive removal of hydrogen :—



$$\begin{tikzcd} CH_4 \arrow[r] & CH_3 \arrow[r] \arrow[d] & CH_2 \arrow[r] \arrow[d] & CH \arrow[r] \arrow[d] & C \\ & C_2H_6 & C_2H_4 & C_2H_2 & \end{tikzcd}$$

and that partial recombination of the free radicles leads to hydrocarbon formation in the absence of sufficient oxygen to effect complete combustion. The liquid form, produced by a pressure of 47 atmospheres at 0°, is sensitive to shock, detonating violently and decomposing into its elements when struck or rapidly heated. The transport of commercial acetylene is accomplished by compressing it into cylinders filled with a porous diatomaceous earth saturated with acetone or, alternatively, by compressing it with ethylene. Under the trade-name ' Narcylene ', pure acetylene has been used as an anæsthetic, although the explosion hazard of a mixture of acetylene and oxygen is too great for the mixture to achieve extended use.

The general properties of some simple alkynes are shown in the table below :—

TABLE XV

Alkyne	M.P.	B.P.	D_4^{20}	n_D^{20}	M.P. of compound, $(C_nH_{2n-1})_2Hg$
Ethyne (acetylene)	− 81·8	sublimes	0·6179 (at b.p.)	—	—
Propyne	− 101·5	− 23·3	0·6714 (at b.p.)	1·3746 (at b.p.)	204
Butyne-1	− 122·5	+ 8·6	0·6682	—	163
Butyne-2	—	27	0·6937	1·3939	—
Pentyne-1	− 98	40	0·695	1·386	118
Pentyne-2	− 101	55	0·713	—	—
Hexyne-1	—	72	0·7195	1·399	96
Heptyne-1	—	99·6	0·7332	1·4083	61
Octyne-1	—	126·0	0·7469	1·4169	80
Nonyne-1	—	151	0·763	1·425	68
Decyne-1	—	182	—	—	80
Octadecyne-1	28	180/15 mm.	0·8025	—	—
Eicosylene (Eicosyne-1) ($C_{20}H_{38}$)	—	314	0·8181	—	—

REACTIONS OF ACETYLENE AND THE ALKYNES

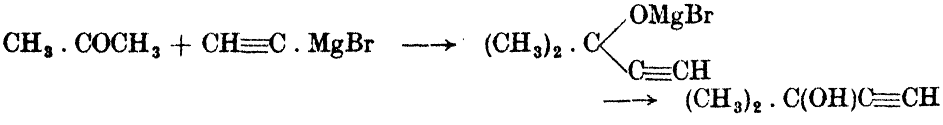
Acetylene and the 1-alkylacetylenes form metallic derivatives with great ease, the hydrogens adjacent to the alkyne carbon atoms being replaceable. Both hydrogen atoms of acetylene are replaceable; only one hydrogen is available in mono-alkyl acetylenes, and the disubstituted acetylenes have no hydrogen available for metal salt formation. The more common metal derivatives of acetylene are :—

The mono- and di-sodium salts. $CH\equiv C . Na$ and C_2Na_2	The former is extremely valuable in synthetic reactions (see below).
The calcium salt CaC_2*	Usually known as 'calcium carbide' and prepared by fusion of lime and coke in an electric furnace.
Magnesium carbide MgC_2*	The formation of a magnesium carbide by the union of magnesium and carbon at high temperatures has been observed, but there is some doubt as to the propriety of expressing its composition by the formula MgC_2, as it is decomposed to propyne $CH_3C\equiv CH$ by water.
Copper acetylide Cu_2C_2	When acetylene is passed into ammoniacal cuprous chloride solution a chocolate coloured precipitate of cuprous acetylide $Cu_2C_2H_2O$ is formed, which, on drying, can be dehydrated to the explosive Cu_2C_2.
Silver and mercury acetylides	Silver, mercuric and mercurous salts are similarly formed, Ag_2C_2, HgC_2, and Hg_2C_2. All are explosive when dry, and are readily decomposed by acids. The statement frequently met with that copper and silver acetylides give pure acetylene with acids is incorrect; pure acetylene can, however, be obtained by the action of solutions of potassium cyanide on copper acetylide.

This ready tendency to form metallic derivatives has led to the conception of acetylene and its analogues as acids; although this is not strictly correct, the replaceable hydrogen not being ionised *per se*, the hydrogen of acetylene is sufficiently labile to react with the alkyl or aryl group of a Grignard reagent, thus :—

$$CH\equiv CH + C_5H_{11}MgBr \longrightarrow C_5H_{12} + CH\equiv C . MgBr$$

Thus, if acetylene be passed through an ethereal solution of amyl magnesium bromide, pentane is evolved and magnesium ethynyl bromide remains in solution. It shows the reactions of a Grignard reagent, e.g. :—



$$CH_3 . COCH_3 + CH\equiv C . MgBr \longrightarrow (CH_3)_2 . C\begin{array}{l}\nearrow OMgBr\\ \searrow C\equiv CH\end{array} \longrightarrow (CH_3)_2 . C(OH)C\equiv CH$$

Lead and mercury organo-halides react with acetylene, but in this case the metal retains its organic radicle, parting with the halogen :—

$$2CH_3HgI + CH\equiv CH \longrightarrow CH_3HgC\equiv CHg . CH_3 + 2HI$$

The compounds produced are crystalline and melt sharply [1], as indicated in the table below :—

[1] Spahr, Vogt and Nieuwland, 1933.

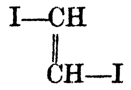
TABLE XVI

R. in $RHgC \equiv CHgR$	M.P.
Methyl	233°
Ethyl	196°
Propyl	157°
i-Propyl	111°
Butyl	126°
sec-Butyl	106°
Amyl	92°
iso-Amyl	107°
Hexyl	105°
Heptyl	96°
Octyl	108°
Nonyl	98°
Decyl	111°

REACTIONS OF ACETYLENE

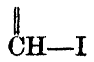
Acetylene does not appear to undergo oxidation in stages short of complete disruption of the molecule. Complete combustion under special conditions gives carbon dioxide and water, but normal burning yields much free carbon, and lampblack has been manufactured by this method. Acetylene is strongly endothermic, its decomposition being brought about readily, and mixtures with air containing any proportion of acetylene from 3 to 82 per cent. explode violently. The endothermic properties of acetylene also find employment in cutting metals, where local production of very high temperatures is necessary; since on combustion acetylene yields more heat than could be obtained by the combustion of the equivalent weights of carbon and hydrogen a very hot flame is obtained.

The reduction of acetylene to ethylene and ethane can be accomplished by direct hydrogenation in the presence of catalysts, but offers no points of interest. Halogens attack acetylene very readily; when chlorine and acetylene are mixed without precaution the halogen removes the hydrogen from the hydrocarbon with explosive violence, leaving carbon. Dilution of the gases with nitrogen, or passage into an inert solvent, leads to a mixture of halides in which tetrachlorethane and dichlorethylene predominate; at the same time, a little substitution takes place and penta- and hexachlorethane are formed. All four products may readily be separated by distillation, and are available in industrial quantities. The action of bromine is not so violent, and the amounts of penta- and hexa-substituted derivatives produced are much smaller than with chlorine. Iodine requires to be heated to 150° to react with acetylene when it gives a mixture of the stereoisomeric diiodoethylenes :—



$$\begin{array}{c} I{-}CH \\ \| \\ CH{-}I \end{array}$$

trans-diiodoethylene
solid



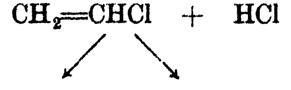
$$\begin{array}{c} CH{-}I \\ \| \\ CH{-}I \end{array}$$

cis-diiodoethylene
liquid

The first stage in the addition of halogen acids to acetylene takes place easily and gives the simple ethylene derivative commonly known as vinyl chloride

$$C_2H_2 + HCl \longrightarrow CH_2{=}CHCl$$

The addition of the second molecule can take place in two ways:



$$CH_2{=}CHCl + HCl$$

$$CH_3 . CHCl_2 \qquad CH_2Cl . CH_2Cl$$

Ethylidene chloride
Ethylene dichloride

In the absence of catalysts, ethylidene chloride is formed according to Markownikov's rule ; peroxide catalysts almost completely reverse the direction of addition leading to ethylene dichloride.

The ability of acetylene to add water under the influence of catalysts has led to the establishment of a considerable industry. Thus, the first step is the

$$\begin{tikzcd}
 & C_2H_2 \arrow[dd, "H_2O"'] & & \\
 & & CCl_3\,.\,CHO \arrow[r] & CHCl_3 \\
CH_3\,.\,CH_2OH & CH_3\,.\,CHO \arrow[l] \arrow[ur, "3Cl_2"] \arrow[r] & CH_3COOH &
\end{tikzcd}$$

passage of acetylene either through a hot saturated solution of mercuric oxide in 5·5 per cent. sulphuric acid, or in strong acid with mercuric salts at 35–40°. In either case acetaldehyde distils out, and is condensed, and serves as the raw material for acetic acid manufacture. The combination can be carried out in the vapour phase at 350–380°, using a boric-phosphoric acid catalyst. The process does not end with the formation of acetaldehyde, but can go a stage further with the formation of crotonaldehyde (butenal-2)

$$CH_3\,.\,CHO + CH{\equiv}CH \longrightarrow CH_3\,.\,CH{=}CH\,.\,CHO$$

It is not contended that the equation above indicates the progress of the addition, which probably involves the unstable vinyl alcohol. An appropriate choice of catalyst enables acetaldehyde or crotonaldehyde to be produced at will.

The addition of hydroxylic compounds to acetylene is not confined to water ; acetic acid reacts in the same way as water to give, first, vinyl acetate, and, if the process be continued, ethylidene diacetate :—

$$CH{\equiv}CH + CH_3COOH \longrightarrow CH_2{=}CHO\,.\,CO\,.\,CH_3 \longrightarrow CH_3CH[O\,.\,COCH_3]_2$$

The process can be controlled to produce vinyl acetate almost exclusively, and the reaction constitutes the method by which vinyl acetate is prepared for plastics manufacture.

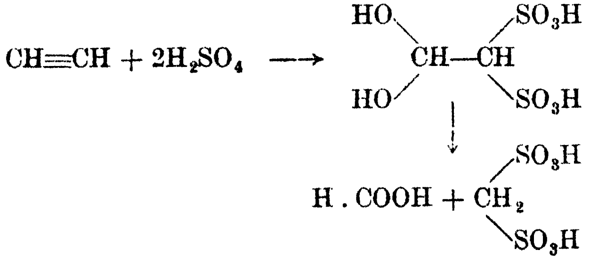
In the same way, alcohols will add to acetylene in the presence of a mercury catalyst to give acetals :—

$$CH{\equiv}CH + C_2H_5OH \longrightarrow CH_2{=}CH\,.\,OEt + C_2H_5OH \longrightarrow CH_3\,.\,CH[OEt]_2$$

Often the addition of fluoroboric acid assists the formation of acetals where the reaction is sluggish, as in the case of the acetal of the half ether of diethylene glycol :—

$$CH{\equiv}CH + 2\,.\,EtO\,.\,CH_2\,.\,CH_2\,.\,O\,.\,CH_2\,.\,CH_2OH \longrightarrow CH_3\,.\,CH[OCH_2CH_2OCH_2CH_2OEt]_2$$

This tendency to addition is strong enough to proceed even with sulphuric acid. With oleum two molecules of acid add to acetylene giving ethane-1, 1-diol-2, 2-disulphonic acid, a substance which is readily broken down by mild alkalies



$$CH{\equiv}CH + 2H_2SO_4 \longrightarrow (HO)_2CH{-}CH(SO_3H)_2 \longrightarrow H\,.\,COOH + CH_2(SO_3H)_2$$

to formic and methane disulphonic acids.

The polymerisation of acetylene is a reaction which has been intensively studied. As long ago as 1862 Berthelot observed the formation of small amounts of benzene from acetylene on heating, and it has been shown by later workers that the pyrolysis of acetylene leads to a whole range of mono- and poly-cyclic aromatic compounds. The controlled polymerisation of acetylene to simple substances was worked out by Nieuwland and others.[1] The products are mono- and di-vinyl acetylene (butenyne-1, 3 and hexadienyne-1, 5, 3). The polymerisation of acetylene to these substances :—

$$2CH{\equiv}CH \longrightarrow CH_2{=}CH\,.\,C{\equiv}CH + CH{\equiv}CH \longrightarrow CH_2{=}CH\,.\,C{\equiv}C\,.\,CH{=}CH_2$$

is carried out by passing acetylene through aqueous solutions of cuprous salts, with ammonium chloride. Control of the conditions allows either substance to be formed, almost to the exclusion of the other.

The two products, butenyne-1, 3 and hexadienyne-1, 5, 3, are interesting examples of hydrocarbons exhibiting both double and triple links. Butenyne-1, 3 is a pleasant smelling liquid, b.p. 5°, and is the basis of a considerable industry, that of the manufacture of Neoprene. When butenyne-1, 3 reacts with hydrochloric acid a chlorbutadiene is obtained, which can be converted to a

$$CH_2{=}CH\,.\,C{\equiv}CH + HCl \longrightarrow CH_2{=}CH\,.\,CCl{=}CH_2$$

rubber-like linear polymer (Neoprene ; see Appendix II). Divinylacetylene (hexadienyne-1, 5, 3) is an isomer of benzene, boiling at 83·5° ; it is explosive and can absorb oxygen from the air to form a violently explosive peroxide. Its linear structure has been proved by catalytic reduction to hexane.

During the formation of the two polymers just discussed, some tetramer is formed (C_8H_8) ; it is probably an octatrienyne-1, 5, 7, 3, but is almost explosively unstable.

The conversion of acetylene into its tetramer, *cyclo*öctatetrene, C_8H_8, can be accomplished readily by catalysts, under pressure. This important reaction is discussed on p. 127.

When acetylene—diluted with about 15 per cent. of nitrogen—is passed over copper bronze at temperatures between 200° and 260°, an unusual polymer is formed as a most voluminous yellow powder. It is called ' cuprene ', and represents the building up of acetylene into a complex, and probably indeterminate, aromatic lattice. Oxidation of cuprene with powerful reagents yields benzoic, phthalic and mellitic acids, and reduction gives aromatic hydrocarbons. It has a limited use as a filler in the manufacture of electrical goods and as a substitute for cork in making linoleum.

THE HOMOLOGOUS ALKYNES

Propyne, more often called allylene because, as an isomer of allene, it is produced with that substance by the action of alcoholic potash on 2, 2-dichlorpropane, is also produced by the action of water on magnesium carbide,[2] and may be prepared from allene (q.v.) by treatment in ether solution with sodium. A simpler way of preparation is the methylation of sodium acetylide in liquid ammonia, using dimethyl sulphate.

$$CH{\equiv}C\,.\,Na + Me_2SO_4 \longrightarrow CH{\equiv}C\,.\,CH_3 + NaCH_3\,.\,SO_4$$

The reactions of propyne are entirely analogous to those of acetylene, making due allowance for the absence of one ' acidic ' hydrogen. Thus, halogens, halogen acids and water all add to the triple bond, giving acetone in the last instance. The halogen acid additions, in general, obey Markownikov's rule. Further, the sodio-derivative of propyne reacts normally with substances containing the CO group. Thus, carbon dioxide yields the sodium salt, butyne-2-acid :—

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[1] Nieuwland, Calcott, Downing and Carter, *J.A.C.S.*, 1931, **53**, 4197.

[2] Keiser, *Am. Chem. J.*, 1896, **18**, 328.

$$CH_3C{\equiv}C\,.\,Na + CO_2 \longrightarrow CH_3\,.\,C{\equiv}C\,.\,COONa$$

Aldehydes give the acetylenic secondary alcohols, e.g., acetaldehyde gives pentyne-2-ol-3 : —

$$CH_3\,.\,C{\equiv}C\,.\,Na + CH_3CHO \longrightarrow CH_3\,.\,C{\equiv}C\,.\,CHOH\,.\,CH_3,$$

whilst the acetylenic aldehydes and ketones may be obtained by the action of formic ester and acyl chlorides respectively :—

(i) $H\,.\,COOEt + CH_3\,.\,C{\equiv}C\,.\,Na \longrightarrow CH_3\,.\,C{\equiv}C\,.\,CHO$ Butyne-2-al

(ii) $C_2H_5\,.\,CO\,.\,Cl + CH_3\,.\,C{\equiv}C\,.\,Na$
$\longrightarrow CH_3C{\equiv}C\,.\,CO\,.\,C_2H_5$ Hexyne-2-one-4

These syntheses, often referred to as Moureu's reactions, are among the most satisfactory ways of building up compounds containing the triple bond.

The reactions are equally adapted to the homologous 1-alkynes ;[1] thus, butyne-1, $CH_3\,.\,CH_2\,.\,C{\equiv}CH$, and all the homologues up to decyne-1 react, and it is interesting to note that the sodio derivatives of heptyne-1 (obtained from castor oil, *via* heptaldehyde) gives a good yield of octyne-2-acid with carbon dioxide. The methyl ester of this acid (industrially referred to as " methyl heptine carbonate ") is a valuable intermediate for building up violet perfumes.

There is a strong tendency for the triple bond in some hydrocarbon chains to move to the terminal carbon. Thus, butyne-2 is a stable substance which, when heated with sodium, is converted to butyne-1, and this reaction is general ; Vaughan, in 1933, showed that the symmetrical diamyl acetylene (dodecyne-6) passed into dodecyne-1 by heating at 210° in the presence of sodamide. This constitutes an interesting method of synthesis of the higher 1-alkynes. Disodium acetylene is allowed to react with an alkyl iodide, to give a symmetrical alkyne which is converted to a 1-alkyne by heating with sodamide :—

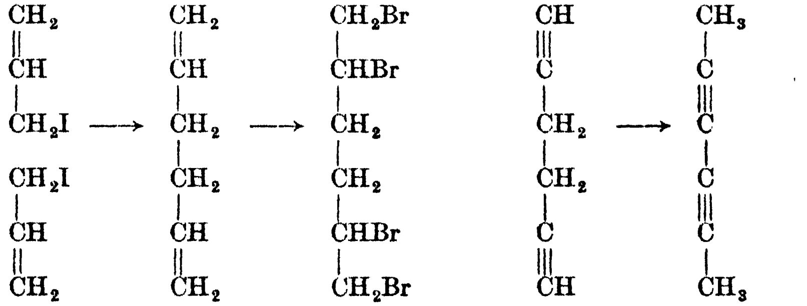
$$2C_6H_{13}I + NaC{\equiv}CNa \longrightarrow C_6H_{13}\,.\,C{\equiv}C\,.\,C_6H_{13} \longrightarrow C_{12}H_{25}C{\equiv}CH$$

The 1-alkynes can be identified by their reaction with mercuric cyanide, which follows the course :—

$$Hg(CN)_2 + 2RC{\equiv}CH \longrightarrow RC{\equiv}C\,.\,Hg\,.\,C{\equiv}C\,.\,R + 2HCN$$

The compounds are crystalline, and have definite melting points which are given in the table (p. 108).

One or two miscellaneous substances containing two triple bonds are of interest, mainly on account of their isomerism with benzene C_6H_6. Thus, hexadiyne-1, 5, made from diallyl (hexadiene-1, 5) by the following reactions :—



Hexadiyne-1, 5
m. – 6°
b. 87°

Hexadiyne-2, 4
m. 64·5°
b. 129°

is a colourless, very unstable liquid, polymerising rapidly and isomerising when heated with alcoholic potash to hexadiyne-2, 4, an extremely stable substance.

---

[1] T. H. Vaughan, *J.A.C.S.*, 1934, **56**, 2064.

ALICYCLIC HYDROCARBONS

There has been a tendency in the arrangement of treatises and other literature of organic chemistry to segregate the cyclic non-aromatic compounds under the heading 'polymethylene derivatives', a procedure which is more convenient than indicative of fundamental differences in properties. The introduction of a cyclic structure only produces serious divergences from normal in the case of 3- and 4-membered rings; hydrocarbons with rings of five or more members, even up to thirty or more, behave normally, and are comparable in general reactions with the paraffins of similar carbon number. Thus, for example, the increase in the molecular heat of combustion of cycloalkanes with five or more methylene groups, produced by an additional —CH_2 group, is the same as that produced by a similar additional group in the paraffin series.

Prior to 1881, when Markownikov and Krestownikov [1] discovered a cyclobutane derivative, the conclusion had been reached that rings with less than five carbon atoms could not exist, a view which was supported by the current concept of the carbon atom as a rigid tetrahedral structure. Successive discoveries of 3- and 4-membered rings by Freund [2] and Perkin [3] conclusively established the fact that 3- or 4-membered carbon rings could exist, and the new knowledge led Baeyer [4] to revise the rigid tetrahedral conception of carbon and its valencies and to formulate his ingenious 'strain theory'. This latter had as its basis the assumption that the normal angle between the 'valencies' of carbon was 169° 28′ (the natural tetrahedral angle) and went on to assume that when a ring was formed 'strain' was set up by deviation of the valencies through an angle which would, of course, depend on the ring size. Thus, in Fig. 1 is shown the deviation of 24°–44′ produced on each carbon valency in a three-membered ring; in the table below is shown the angle of

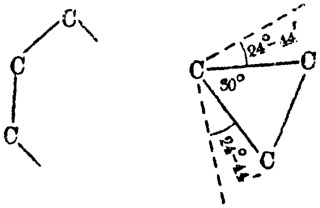


FIG. 1.

TABLE XVII

	No. of member in ring (N)	Deviation of angle (degree of strain)	Mol. heat of combustion (H)	Excess heat of combustion (E)*
Ethylene	2	54° . 44′	340	28 (26)
*Cyclo*propane	3	24° . 44′	505	37 (34)
*Cyclo*butane	4	9° . 44′	662	30 (26)
*Cyclo*pentane	5	0° . 44′	795	15 (10)
*Cyclo*hexane	6	— 5° . 16′	948	12 (6)
*Cyclo*heptane	7	— 9° . 33′	1106	14 (7)
*Cyclo*decane	10	— 17° . 16′	1586	26 (16)
*Cyclo*pentadecane	15	— 23° . 16′	2355	15 (0)
*Cyclo*heptadecane	17	— 24° . 41′	2669	17 (0)
*Cyclo*triacontane	30	— 29° . 16′	4680	nil (— 30)

* Obtained by E = H — Nh (where *h* is the normal heat of combustion (156) for the CH_2 group in paraffins). (Figures in brackets from *h* = 157.)

---

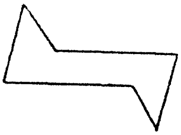
[1] Markownikov and Krestownikov, *Ann.*, 1881, **208**, 333.

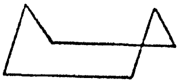
[2] Freund, *Monatsh.*, 1882, **3**, 626.

[3] Perkin, *Ber.*, 1883, **16**, 1793.

[4] Baeyer, *Ber.*, 1885, **18**, 2277.

deviation of a series of cycloalkanes up to *cyclo*-triacontane, together with the molecular heats of combustion and the excess heat of combustion over the theoretical figure calculated as a multiple of the figure associated with the —CH_2 group. It was argued from the first few figures of this table that the 'strain' showed itself by an enhanced heat of combustion, but the implication is not entirely clear, especially as the calorimetric values cannot be guaranteed to an accuracy of more than 1 per cent. It is, however, true that rings containing three and four members appear to be less easy of production than those containing five and six members, but in spite of the plausible nature of the 'strain theory' there is little evidence to show that such 'strain' exists, even in smaller rings; if *cyclo*-propane were a highly strained structure, one would scarcely expect it to be indifferent to the action of permanganate and substituted by chlorination without ring fracture. Even if it be admitted that there is some qualitative justification for a strain theory in relation to 3- and 4-rings, such theory cannot apply to other rings, since it is erroneously based on the assumption that large rings are planar. This is not correct, and although the fact was pointed out in 1890 by Sachse,[1] Baeyer's theory continued to dominate the field. Mohr, about twenty years ago, developed the non-planar concept of ring structure, and it has been confirmed by experimental isolation of the stereoisomeric forms implied by the non-planar nature of rings. Thus, cyclohexane can have two space forms :—





and the view is now accepted that the large rings are virtually strainless. The stereoisomeric implications of this view are discussed in Vol. III. Further discussion of large rings is given in Appendix I to Chapter VI.

Alicyclic Compounds of Natural Occurrence

Petroleum usually contains an appreciable proportion of alicyclic hydrocarbons, mainly alkyl derivatives of cyclopentane and cyclohexane, which are usually called 'naphthenes'. Thus, the straight run gasolines (light petroleum fractions) from Californian petroleum contain up to 40 per cent. naphthenes, and most Texan and Pennsylvanian straight run gasolines contain 20–25 per cent. The principal constituents of the naphthene fraction are :—

Cyclopentane
Methylcyclopentane
1, 1-Dimethylcyclopentane
Cyclohexane
Methylcyclohexane
1, 2-, 1, 3- and 1, 4-Dimethylcyclohexane
1, 2, 4-Trimethylcyclohexane

Petroleum chemists refer to methylcyclohexane as a 'heptanaphthene', to the dimethylcyclohexanes as 'octanaphthenes'. Any nine or ten carbon alicyclic hydrocarbons are also called 'nonanaphthenes' and 'decanaphthenes'; small amounts of decanaphthene and undecanaphthene fractions have been isolated from petroleum and contain the dimethyl ethyl cyclohexanes and higher analogues. In addition, a smaller proportion of bicyclic naphthenes are present,[1] derived from bicyclopentane (61) and decahydronaphthalene (62).

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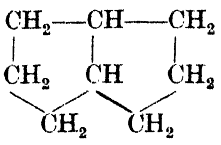
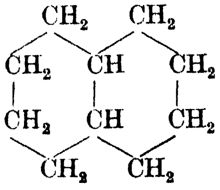
[1] Sachse, *Ber.*, 1890, **23**, 1363.



(61)



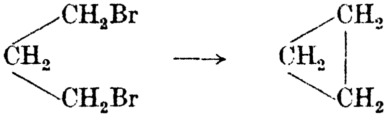
(62)

The alicyclic hydrocarbons also figure largely in the field of terpene chemistry, and are discussed from this standpoint in Chapter VIII.

Preparation of Alicyclic Hydrocarbons

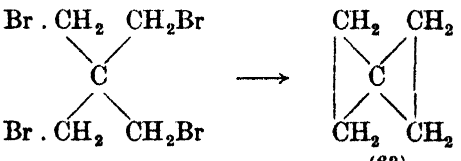
Methods of preparation of alicyclic hydrocarbons may be divided into two main groups (*a*) methods of inducing direct ring formation in hydrocarbon structures, and (*b*) the conversion of oxygenated compounds in which ring structure is already present, to the hydrocarbon.

Most methods of inducing ring formation are variants of the methods used for building up paraffin hydrocarbons. Thus, the Würtz reaction can be used on a dibromide to yield an alicyclic hydrocarbon :—



Sodium, zinc in alcohol, or zinc in the presence of sodium iodide are used to effect the removal of the halogen. The yields of derived product seldom reach more than 50–60 per cent. since, as with the original Würtz reaction, other substances are easily produced.

It is interesting to note that the removal of bromine from 1, 3-dibrompropane by zinc, as illustrated above, is analogous to the removal of two adjacent halogens by zinc from ethylene dibromide to give ethylene. The remarkable fact is that this reaction goes much more easily with ethylene dibromide than with propylene dibromide—and does not proceed with 1, 4-dibrombutane, and is not, therefore, available for the preparation of cyclobutane. This is in exact opposition to the strain theory which predicts a progressive increase of ease of formation from ethylene to cyclo-butane. In general, cyclo-butane rings, especially those not containing a carbonyl group, are difficult to prepare ; probably more difficult than any other type. They are occasionally obtained by reactions calculated to produce an aggregate of cyclo-propane rings. Thus, Gustavson, in 1896, attempted to obtain a simple spiro-hydrocarbon (63)



(63)

from the appropriate dibromide, and obtained a mixture of two cyclobutane derivatives, 1-methyl cyclobutene-1 and methylene cyclobutane.

Polymerisation is a fruitful source of alicyclic hydrocarbon structure, as also is the addition of hydrocarbons under the conditions of the Diels-Alder reaction. Ring formation from the simple unsaturated hydrocarbons is uncommon, but with enynes the reaction is common ; thus, hexadienyne-1, 5, 3 (64) is readily converted to 5 : 8-*cyclo*dodecadiene-1, 11-diyne-3, 9 (1, 2-bis (butenynyl) *cyclo*butane) (65) :—

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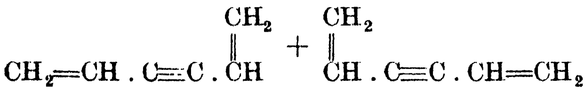
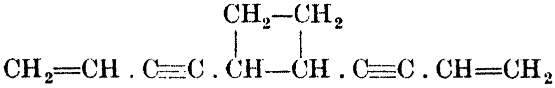
[1] Coates, *J.A.C.S.*, 1906, **28**, 384 ; Ross and Leather, *Analyst*, 1906, **31**, 284.



$$\begin{array}{ccccc} & \mathrm{CH_2} & & \mathrm{CH_2} & \\ & \| & + & \| & \\ \mathrm{CH_2{=}CH\,.\,C{\equiv}C\,.} & \mathrm{CH} & & \mathrm{CH} & \mathrm{.\,C{\equiv}C\,.\,CH{=}CH_2} \end{array}$$

(64)



$$\begin{array}{ccccc} & \mathrm{CH_2} & - & \mathrm{CH_2} & \\ & | & & | & \\ \mathrm{CH_2{=}CH\,.\,C{\equiv}C\,.} & \mathrm{CH} & - & \mathrm{CH} & \mathrm{.\,C{\equiv}C\,.\,CH{=}CH_2} \end{array}$$

(65)

Other methods for preparing *cyclo*alkanes are, in general, the normal reactions used for converting ketones, alcohols, or acids to the hydrocarbons ; the preparation of the oxygen compounds is discussed in the appropriate chapters. (See Chapters V, VI and VII.)

The physical properties of the *cyclo*alkanes are shown in the table below :—

TABLE XVIII

Name	Formula	M.P.	B.P.
*Cyclo*propane	C_3H_6	— 127°	— 35°
*Cyclo*butane	C_4H_8		+ 12°
*Cyclo*pentane	C_5H_{10}		50·5°
*Cyclo*hexane	C_6H_{12}	+ 7°	81°
*Cyclo*heptane	C_7H_{14}	— 12°	117°
*Cyclo*octane	C_8H_{16}	+ 11·5°	148°
*Cyclo*decane	$C_{10}H_{20}$	9·6°	201°
*Cyclo*dodecane	$C_{12}H_{24}$	61°	
*Cyclo*tetradecane	$C_{14}H_{28}$	53°	
*Cyclo*pentadecane	$C_{15}H_{30}$	37°	
*Cyclo*hexadecane	$C_{16}H_{32}$	57°	
*Cyclo*heptadecane	$C_{17}H_{34}$	63°	
*Cyclo*docosane	$C_{22}H_{44}$	46°	
*Cyclo*tetracosane	$C_{24}H_{48}$	47°	
*Cyclo*hexacosane	$C_{26}H_{52}$	42°	
*Cyclo*octacosane	$C_{28}H_{56}$	48°	
*Cyclo*triacontane	$C_{30}H_{60}$	56°	

*Cyclo*propane, discovered by Freund in 1882, is a pleasant-smelling gas, which has been used as a general anaesthetic in place of chloroform/ether mixtures. It possesses the advantages of being almost non-irritant, and since 7 per cent. in the respired air is sufficient to cause anaesthesia there is little danger of asphyxiation from oxygen-deprivation. Its cost has hindered its use ; it is usually prepared by heating 1, 3-dibromopropane with sodium.

Chemically, *cyclo*propane is reactive ; heated alone, it isomerises to propylene ; it is readily reduced to propane by hydrogen, even at temperatures of 70–80° in the presence of nickel or platinum. Halogens react readily with *cyclo*propane ; chlorine in diffused light yields the substitution product chloro*cyclo*propane, a pleasant smelling liquid, b. 44°. Some di- and tri-chloropropanes are produced at the same time, together with 1, 1-dichloro*cyclo*propane,[1] a colourless heavy liquid, b. 75–76°. Bromine, on the other hand, reacts rapidly with *cyclo*propane to give 1, 3-dibromopropane as the sole product. *Cyclo*propane is stable to cold alkaline permanganate, thus offering a distinguishing point between cyclic unsaturation and ethylenic unsaturation. Hydriodic acid opens the *cyclo*propane ring giving propyl iodide.

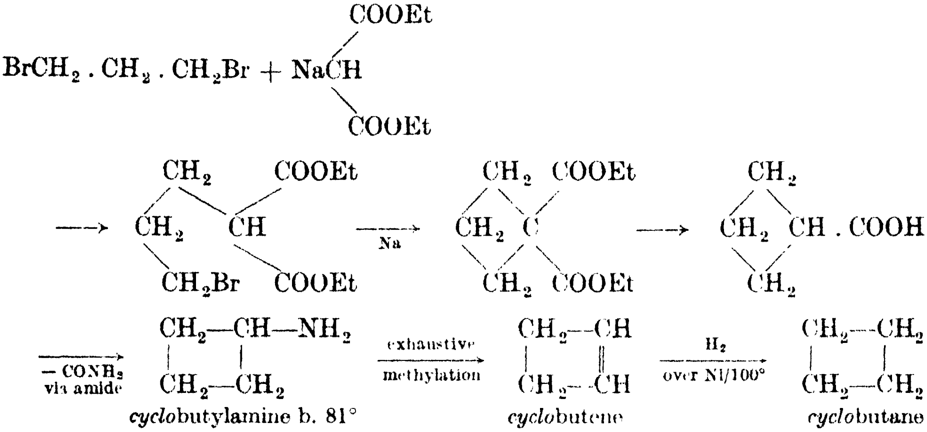
---

[1] Gustavson, *J. Pr. Chem.*, 1890 (2), **42**, 495 ; 1891 (2), **43**, 396 ; 1892 (2), **46**, 159 ; 1894 (2), **50**, 380.

The homologues of *cyclo*propane—methyl*cyclo*propane, b. 5°, and 1, 1-dimethyl*cyclo*propane, b. 21°—behave similarly, and show the differences indicated between chlorination and bromination.

The ring of *cyclo*propane is readily opened by sulphuric acid,[1] which absorbs about 500 vols. of *cyclo*propane at 15° C., and on dilution of the product and distillation, propyl alcohol is obtained.

*Cyclo*butane.—Willstatter, in 1907, devised the following method for making *cyclo*butane, which is sufficiently indicated by the formulæ below :—

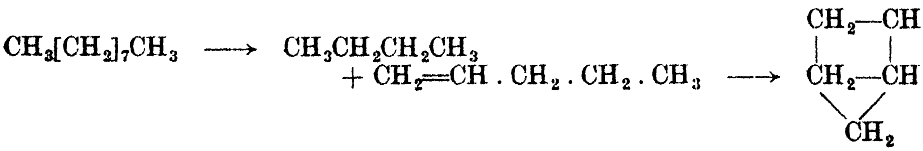


The method is cumbrous and the overall yield is small, but this is almost the only method available for the preparation of these hydrocarbons. Our knowledge of them is scanty ; *cyclo*butane is a liquid, b. – 12°, of pleasant odour. Its chemical properties have not been investigated thoroughly but it has been established that it is not oxidised by cold permanganate ; that it may be hydrogenated catalytically to butane ; and is unaffected by cold hydriodic acid.

The substances methylene *cyclo*butane (b. 41°) and methyl *cyclo*butane from the reduction of pentærythritol tetrabromide are better known, and have been the subject of various researches on their thermal decomposition.[2, 3]

*Cyclo*PENTANE AND ITS HOMOLOGUES

*Cyclo*pentane, a limpid liquid, b. 50·5°, is present in petroleum from a variety of oil-fields. It is also obtained by heating nonane with aluminium chloride,[4]



and can be isolated from this mixture. It is unaffected, even by several days' boiling with anhydrous aluminium chloride, and constitutes one of the most stable hydrocarbons. The synthesis of pure *cyclo*pentane may be accomplished by the action of zinc on 1, 5-dibromopentane or by reducing the readily accessible *cyclo*pentanone.

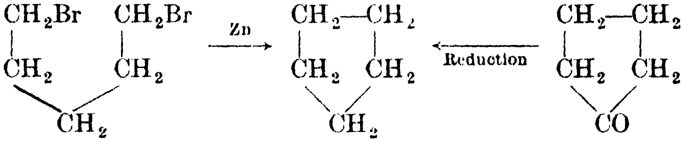
---

[1] Gustavson, *J. Pr. Chem.*, 1887 (2), **36**, 300.

[2] Rozanov, *J. Russ. Phys.-Chem. Soc.*, 1929, **61**, 2291.

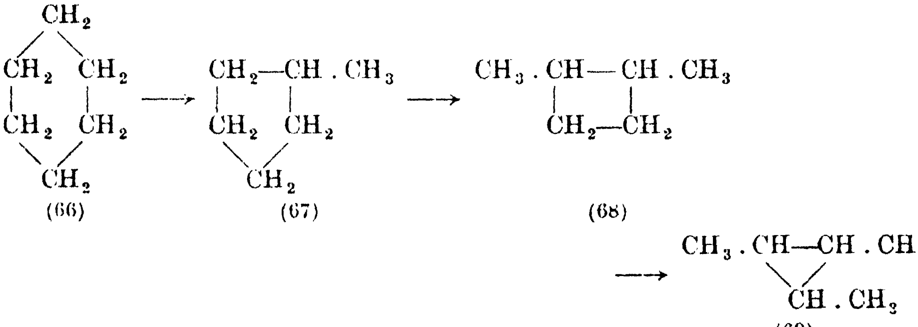
[3] Filipov, *ibid.*, 1914, **46**, 1141.

[4] Cox, *Bull. Soc. Chim.*, 1925, **37**, 1549.



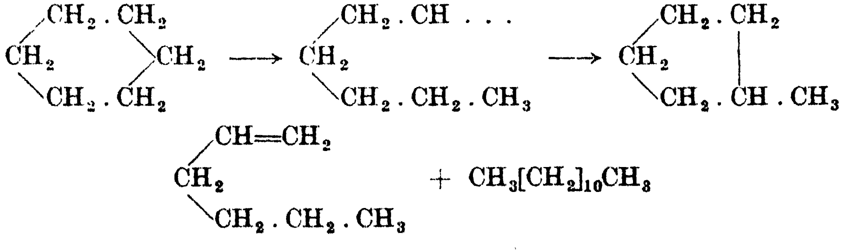
The ring of *cyclo*pentane is opened only with the greatest difficulty, and it is undoubtedly the most stable cycloalkane. Its inertness towards anhydrous aluminium chloride has already been mentioned ; it is unaffected by hydrogen, with or without catalysts, at 300°. Little or nothing is known concerning the chlorination of *cyclo*pentane ; bromine reacts only in sunlight and mono- and dibromo-substitution products are obtained. Nitration can be effected by the use of concentrated acid at low temperatures, or by dilute nitric acid at 100–110° ; there is a strong tendency towards opening the ring with the formation of glutaric acid.

Methyl*cyclo*pentane, pleasant smelling liquid, b. 71°, is more frequently met with than the parent body. In the presence of catalysts, *cyclo*hexane (66) isomerises to methyl*cyclo*pentane (67) on heating at ordinary pressures ; in the absence of a catalyst the same result may be accomplished by heating under pressure.[1]


(66) (67) (68)

(69)

This reaction (often called an ‘ extrusion ’ reaction) is merely part of a general series of such changes the full range of which is indicated above. It will be noticed that the progressive extrusion of a carbon atom leads to 1, 2-dimethyl *cyclo*butane (68), and finally to 1, 2, 3-trimethyl*cyclo*propane (69). This series of reactions, which takes place in the presence of aluminium halides, is another instance of the failure of the so-called ‘ strain theory ’ to co-ordinate the tendencies in ring formation.[2] The mechanism of the reaction is obscure, but probably involves a disproportionating proton change with opening of the ring as shown below :—



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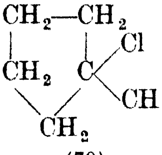
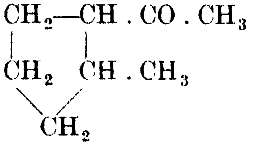
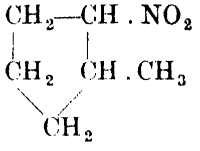
[1] Ipatiov and Dowgelewisch, *Ber.*, 1911, **44**, 2987.
[2] Zelinsky and Turova-Pollak, *ibid.*, 1932, **65**, 1171.

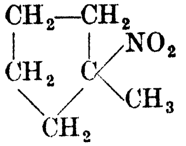
The simultaneous formation of dodecane and hexene-1 supports this view. The reaction is a general one and Willstätter and Kametaka [1] have shown that *cyclo*heptane yields successively methyl *cyclo*hexane and dimethyl *cyclo*pentane by extrusion, and Zelinsky and Freimann [2] that *cyclo*öctane gives methyl *cyclo*heptane and dimethyl*cyclo*hexane under similar circumstances.

The presence of a tertiary carbon atom in the alkyl *cyclo*pentanes makes them much more reactive than *cyclo*pentane itself. Thus, chlorination of methyl*cyclo*pentane [3] yields a mixture containing a preponderance of the 1-chloro-1-methyl derivative (70).


(70)

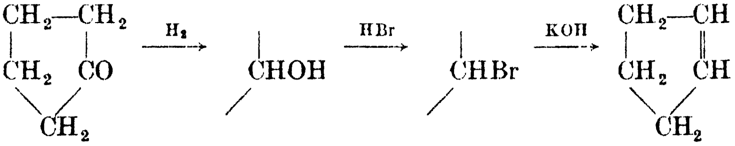

(71)


sec-nitro compound
b. 99°/40 mm.
Sol. in NaOH soln.
(72)


ter-nitro compound
b. 92°/40 mm.
Insol. in NaOH soln.
(73)

On the other hand, acyl chlorides attack methyl*cyclo*pentane in the '2' position giving (2-methyl *cyclo*pentyl) methyl ketone (71). Dilute nitric acid (S.G. 1·075) acts on methyl*cyclo*pentane at 115–120° to give a mixture of the 1- and 2-nitro-compounds (73) and (72).[4]

*Cyclo*pentene, a mobile liquid of penetrating odour, b. 45°, may be obtained by the usual methods from cyclopentanone,



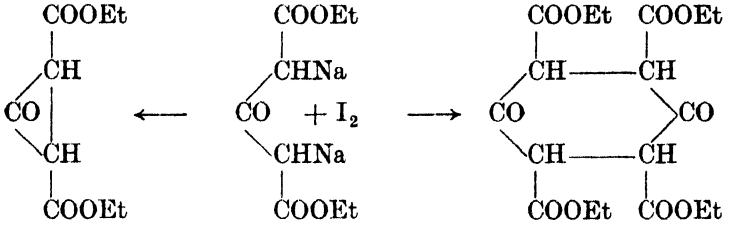
Its properties are essentially those of an olefine.

*Cyclo*HEXANE AND ITS ANALOGUES

*Cyclo*hexane itself, together with its methyl and dimethyl derivatives, are found consistently in petroleum, especially Caucasian and Galician oils. Of the various older methods for preparing *cyclo*hexane, such as the elimination of carbon dioxide from hexahydrobenzoic acid or the reduction of *cyclo*hexanone, few present any points of interest; they are seldom used. The older method of reduction by sodium with ethyl or amyl alcohol served as a basis for the classical researches of Baeyer on the hexahydrophthalic acids, and of Perkin on terpenes from the hexahydrotoluic acids; it is only since the commencement of the present century that the catalytic methods of Sabatier have displaced the older process. One method of producing *cyclo*hexane derivatives is the attempted preparation of *cyclo*propane derivatives by ring closure. Thus v. Pechmann,[5] in attempting to prepare a *cyclo*propane derivative (74) by the action of iodine on the disodium derivative of acetone dicarboxylic ester (75), obtained the *cyclo*hexane derivative (76):—

---

[1] Willstätter and Kametaka, *Ber.*, 1908, **41**, 1480.
[2] Zelinsky and Freimann, *ibid.*, 1930, **63**, 1485.
[3] Markownikov, *Ann.*, 1899, **307**, 335.
[4] Kishner, *J. Pr. Chem.*, 1897, **56**, (2), 369.
[5] v. Pechmann, *Ber.*, 1897, **30**, 2569.



(74) (75) (76)

Pentanone-3-diacid, 1, 5 diethyl ester (di-sodio derivative)

Cyclohexane-1, 4-dione-2, 3, 5, 6-tetracarboxylic acid ethyl ester

*Cyclo*hexane is largely manufactured by the reduction of benzene with hydrogen. This reaction takes place at ordinary temperatures in glacial acetic acid, in the presence of platinum or palladium black. With Raney nickel the reaction requires a temperature of 85–100° ; with the older type of Sabatier-Senderens nickel catalyst 180–230° is needed. All these catalysts are immediately poisoned by traces of thiophen, from which the benzene must be most carefully purified.

*Cyclo*hexane is a colourless liquid of pleasant odour, b. 81°, which exhibits great stability, although in general it is more easily attacked than *cyclo*pentane. Thus, the action of anhydrous aluminium chloride on *cyclo*pentane is negligible ; *cyclo*hexane is converted to a series of smaller ring compounds (see p. 119). Permanganate oxidises *cyclo*hexane to adipic acid, and fuming sulphuric acid oxidises the ring to benzene which is immediately sulphonated.

The chlorination of *cyclo*hexane has been the subject of extensive study from the time of Markownikov in 1898, up to the present time. Using moist chlorine in diffused sunlight Markownikov [1] obtained monochloro*cyclo*hexane. Sabatier and Mailhe [2] obtained the following products :—

	b	d_0^0	
Monochloro*cyclo*hexane	141·6-142·6°/749 mm.	1·0161	
Dichloro*cyclo*hexane (*a*)	105·4-106·4°/50 mm.	1·2056	
Dichloro*cyclo*hexane (*b*)	106·4-107·4°/50 mm.	1·2060	
Trichloro*cyclo*hexane liquid (*a*)	139·5-141·5°/50 mm.	1·3535	
Trichloro*cyclo*hexane liquid (*b*)	143·5-145·5°/50 mm.	1·3611	
Trichloro*cyclo*hexane solid (*c*)	150·4-151·4°/50 mm.	1·5103	m. 66°

The chlorinated *cyclo*hexanes are valuable sources of the semibenzenoid rings as they lose halogen acid on boiling with quinoline. Thus, monochloro *cyclo*hexane gives a good yield of *cyclo*hexene, and the dichlor- derivatives are converted to *cyclo*hexadiene.

Reference has already been made to the progressive conversion of *cyclo*hexane by aluminium chloride to methyl *cyclo*pentane and to dimethyl*cyclo*butane. This reaction, when carried out in the presence of an acyl chloride such as acetyl or benzoyl chloride, gives the acyl derivative of methyl*cyclo*pentane. At the same time some *cyclo*hexane is converted to an unsaturated hydrocarbon, $C_{12}H_{22}$ and a corresponding amount of acyl chloride is reduced to the aldehyde.[3] An interesting and unusual extension of this reaction is the condensation of *cyclo*hexane and ethylene oxide in the presence of aluminium chloride to give hydroxyethyl*cyclo*hexane (77).

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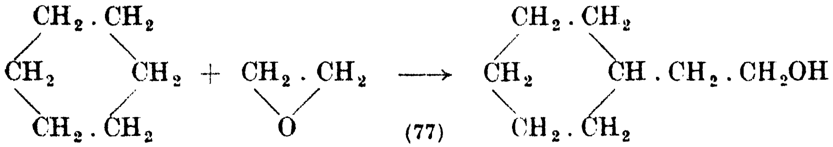
[1] Markownikov, *Ann.*, 1898, **302**, 1.

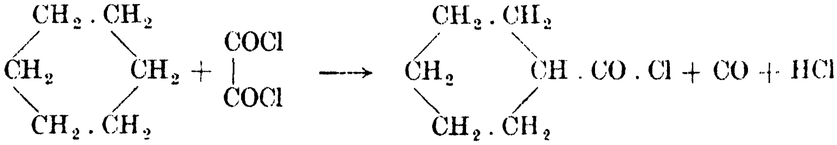
[2] Sabatier and Mailhe, *C.R.*, 1903, **137**, 240 ; *Ann. Chim.*, 1907 (8), **10**, 531.

[3] Nenitzescu, Isăcescu and Ionescu, *Ann.*, 1931, **491**, 189, 210.



(77)

Good yields[1] of hexahydrobenzoyl chloride (78) can be obtained by the action of oxalyl chloride on *cyclo*hexane in sunlight or light from a U.V. lamp. The reaction proceeds :—

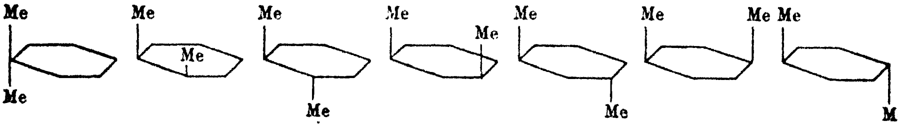


(78)

At ordinary temperatures, *cyclo*hexane is unaffected by the usual nitration mixtures and on raising the temperature oxidation to adipic acid, and not nitration, ensues. The use of dilute nitric acid at 100–150° gives nitro*cyclo*hexane, but not in good yield. The best method of nitrating paraffins and *cyclo*alkanes is by Nametkin's[2] method. In this the *cyclo*hexane is mixed with three parts of hydrated aluminium nitrate and heated to 115–120°. A yield of about 60 per cent. is obtained. The use of aluminium nitrate $[Al(NO_3)_3 . 9H_2O]$ as a nitrating reagent is based on its ability to maintain an equilibrium concentration of nitric acid at temperatures above its melting point. Thus, as long as any undecomposed nitrate remains, the system will be supplied with nitric acid at a fixed concentration, however rapidly it may be taken up by the process of nitration. During all nitrations of *cyclo*hexane some *cyclo*hexanone is obtained, together with a crystalline dinitrodi*cyclo*hexyl, m. 216·5–217°.

HOMOLOGUES OF *Cyclo*HEXANE

Methyl and ethyl *cyclo*hexanes form a substantial part of the naphthene fraction of petroleum. The monomethyl derivative is a pleasant smelling liquid, b. 103°. It is best obtained by the catalytic reduction of toluene by Sabatier's method. The dimethyl *cyclo*hexanes are all known, and constitute

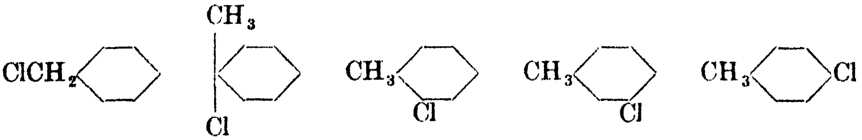


1, 1- or '*gem*' *cis*-1, 2 *trans*-1, 2 *cis*-1, 3 *trans*-1, 3 *cis*-1, 4 *trans*-1, 4

The dimethyl *cyclo*hexanes

a series of seven compounds (structures indicated above). One of the most important members of the series is 1-methyl-4-isopropyl *cyclo*hexane—often called *p*-menthane. It is one parent of the large family of terpenes (see Chap. VIII).

The action of halogens on the substituted *cyclo*hexanes has been widely studied, and Sabatier and Mailhe[3] prepared all five monochloromethyl*cyclo*hexanes :—



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[1] Kharasch and Brown, *J.A.C.S.*, 1940, **62**, 454 ; 1942, **64**, 329.

[2] Nametkin, *J. Russ. Phys.-Chem. Soc.*, 1908, **40**, 1570.

[3] Sabatier and Mailhe, *C.R.*, 1905, **140**, 840.

in order to ascertain the nature of the products produced by the direct chlorination of methyl *cyclo*hexane. They concluded that the 1-chloro-1-methyl product was absent from the mixture, which contained about 60 per cent. of 3-chloro-1-methyl *cyclo*hexane and 40 per cent. of the 2-chloro-body.

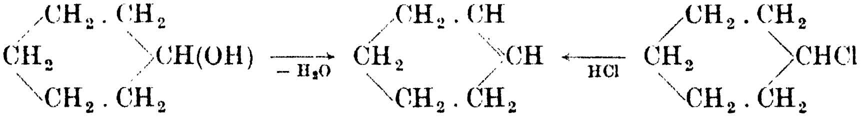
When aluminium chloride is used as a catalyst in the chlorination of substituted *cyclo*hexanes there is some tendency to form the corresponding aromatic compound by loss of hydrogen chloride. This tendency is even more pronounced in the case of the action of bromine in the presence of aluminium bromide, and the isolation of the brominated alkylbenzenes is used as a method of identification of the naphthenes.[1] Common examples are shown in the table below :—

TABLE XIX

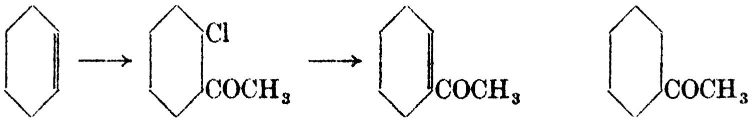
Naphthene	Aromatic bromo-compound	M.P.
1, 3-Dimethyl*cyclo*hexane	Tetrabrom-*m*-xylene	246°
1, 4-Dimethyl*cyclo*hexane	Tetrabrom-*p*-xylene	253°
1, 2, 4-Trimethyl*cyclo*hexane	Tribrom-*ψ*-cumene	254°
1, 3-Dimethyl-5-ethyl*cyclo*hexane	2, 4, 6-Tribrom-1, 3-dimethyl-5-ethylbenzene	218–220°

UNSATURATED HYDROCARBONS OF THE *Cyclo*HEXANE SERIES

The simplest member of this series, *cyclo*hexene, is prepared on an industrial scale by dehydrating *cyclo*hexanol by passage of its vapour over heated alumina ; an alternative method is to remove hydrogen chloride or bromide from monochloro- or monobromo*cyclo*hexane, a stage easily accomplished, almost quantitatively by boiling with quinoline :—



It is a mobile liquid, b. 83°, showing all the properties of unsaturation associated with ethylenic hydrocarbons. Its additions, reductions and oxidations are all regular ; the addition of acetyl chloride in the presence of anhydrous aluminium chloride to give 1-chloro-2-acetyl *cyclo*hexane (1-chloro-1 : 6-*cyclo*-octanone-7) (79) is unusual,[2] but the subsequent ready conversion of this to methyl*cyclo*hexenylketone (80) is to be expected from the labile nature of halogen atoms in the fully saturated rings



(79) (80) (81)

When this reaction is done in a solvent (such as *cyclo*hexane), the *cyclo*hexylmethyl ketone is obtained (81). The hydrogen comes from reduction of the solvent, di-*cyclo*hexyl being simultaneously produced.[3]

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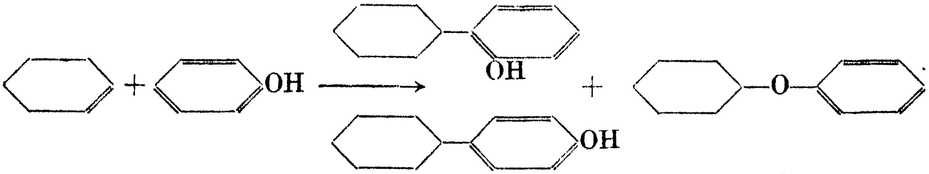
[1] Morgan, *J.S.C.I.*, 1932, **51**, 67T.

[2] Darzens, *C.R.*, 1910, **150**, 707.

[3] Nenitzescu and Cioranescu, *Ber.*, 1936, **69B**, 1820.

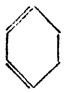
*Cyclo*hexene[1] also condenses with phenol in the presence of anhydrous aluminium chloride to give *o*- and *p*-*cyclo*hexylphenol :—



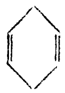
(82)

some *cyclo*hexylphenyl ether is also formed (82).

There are two possible *cyclo*hexadienes (the 1, 2- and 1, 4-dihydrobenzenes) (83) and (84). Little is known of the 1, 4-isomer, but both forms appear to be

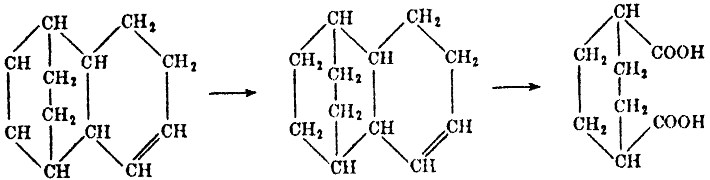


(83)



(84)

produced when the appropriate dichloro- or dibromo-derivatives are treated with alcoholic alkali. The 1, 3-compound always predominates, and is a powerfully odorous liquid, b. 82–83°. (It may be noted in passing that *cyclo*hexane, *cyclo*hexene, *cyclo*hexadiene, and benzene all boil at approximately the same temperature, viz., 81°, 83°, 83°, 80·4° C.) It is doubtful whether the 1, 4-compound has been isolated in pure form. As might be expected from its conjugated double bonds, 1, 3-*cyclo*hexadiene is very reactive. Thus, it forms a dimer (85) by Diels-Alder condensation, the constitution of which was elucidated by Alder and Stein[2] by oxidation of its dihydro derivative (86) to *cis*-hexahydroterephthalic acid (87), thus demonstrating the existence of an endo-ethylene link.



(85) (86) (87)

The dimer has the properties of a terpene hydrocarbon (q.v.), and is a pleasant smelling liquid. The presence of a butadiene group in *cyclo*hexadiene prompts enquiry as to whether it can polymerise like that substance. Hofmann and Damm[3] showed that a rubber-like polymer was obtained on heating *cyclo*hexadiene to 200–220° for several hours, although sodium is without influence on the reaction.

SEVEN AND EIGHT-MEMBERED *Cyclo*ALKANES

Research on the rings larger than *cyclo*hexane was discouraged by the conclusions of Baeyer, who from his ‘ strain theory ’ predicted a progressive degree of strain and instability in rings with more than six members. His assumption that all the carbon atoms of the ring are in one plane was unjustified, and from considerations such as the existence[4] of four stereoisomeric decahydronaphthols, it became apparent that the larger rings are non-planar ; in addition, from the work of Ruzicka[1] on the synthesis of larger ring ketones, it has become clear that there are no limits to ring size set by considerations of strain. In spite of this, however, seven- and eight-membered rings are uncommon; the researches of Pfau[2] have shown that the seven-membered ring does occur in a few natural substances, such as the azulenes (89) and (90) from essential oils of the chamomile family.

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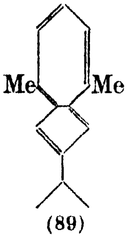
[1] Bodroux, *Ann. Chim.*, 1929 (10), **11**, 511.

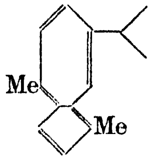
[2] Alder and Stein, *Ann.*, 1932, **496**, 197.

[3] Hofmann and Damm, ‘ Mit schlesischen Kohlenforsch ’. Kaiser-Wilhelm Ges. 1925, **2**, 97 ; see *Chem. Abs.*, 1928, **22**, 1240.

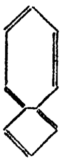
[4] Hückel, *Ann.*, 1927, **451**, 109.



(89)
Vetivazulene

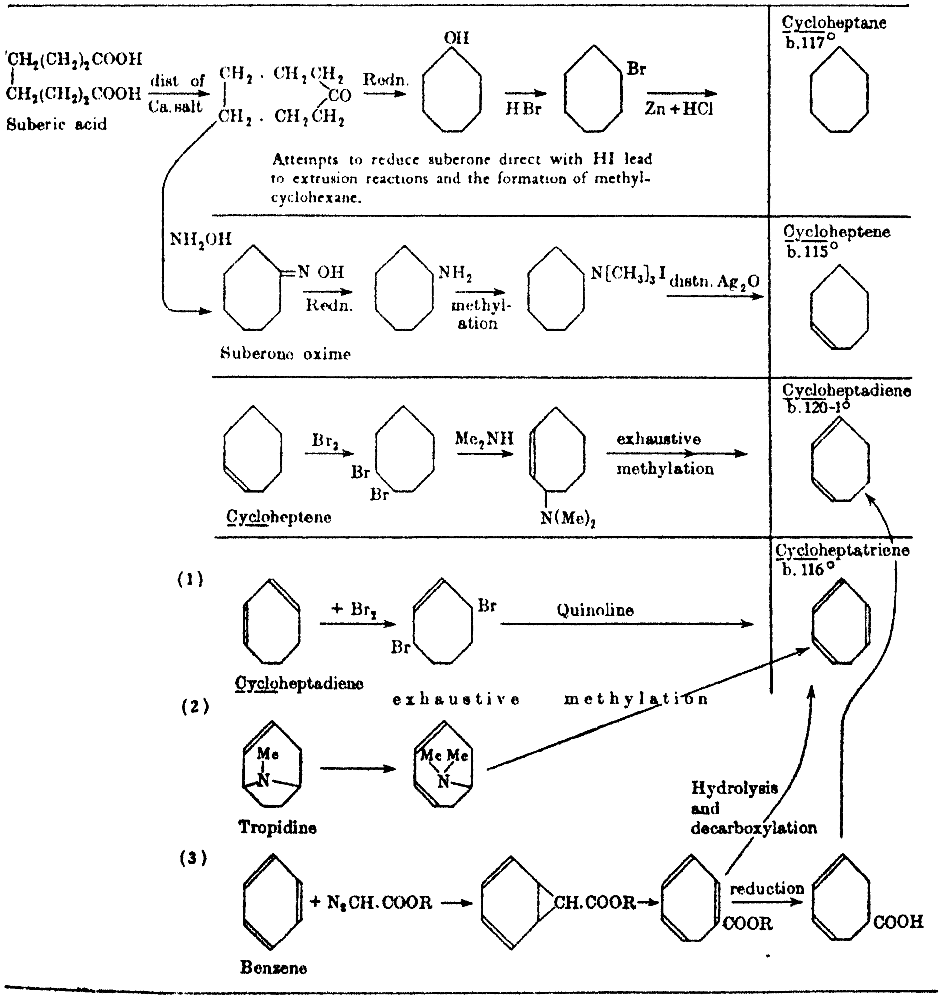


(90)
s-Guaiazulene



Azulene
(91)

TABLE XX.



Attempts to reduce suberone direct with HI lead to extrusion reactions and the formation of methylcyclohexane.

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[1] Ruzicka *et al.*, *Helv. Ch. Acta.*, 1926, **9**, 249–339; 1928, **11**, 670, 1174; 1930, **13**, 1152; 1932, **15**, 1220; 1933, **16**, 493.

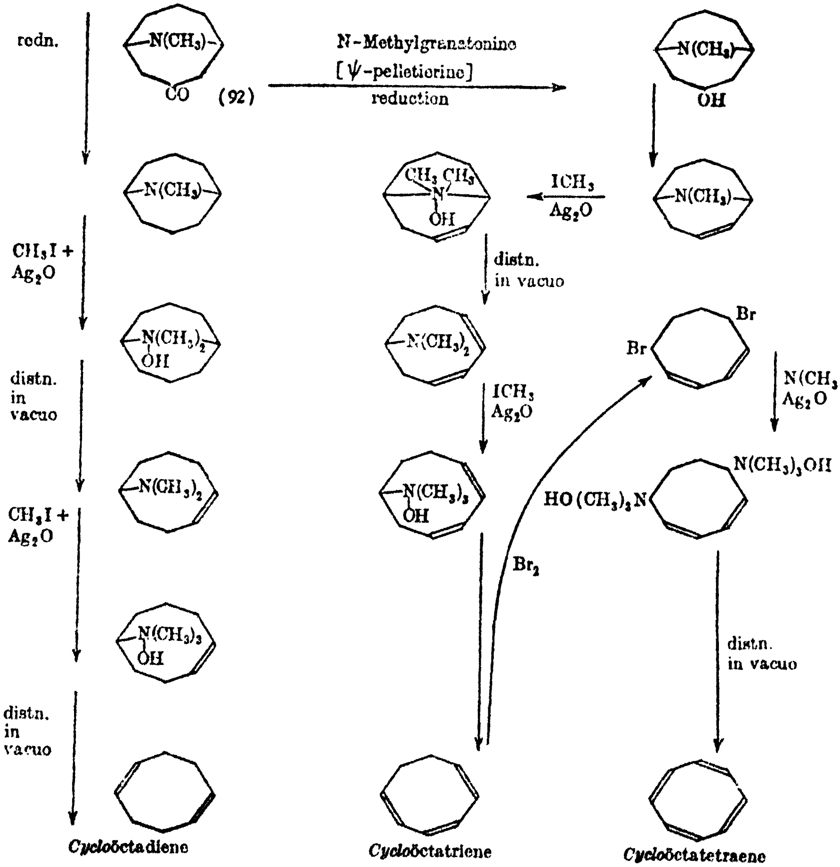
[2] Pfau and Plattner, *ibid.*, 1936, **19**, 858; 1937, **20**, 224.

The parent hydrocarbon, azulene (91), as isomer of naphthalene has been prepared from bicyclo[5 . 3 . 0]decanol-4 by passage of the vapour over palladium-charcoal at 300–350°. All three substances are blue liquids.

The simple *cyclo*heptane derivatives are largely synthetic, and may be obtained by various manipulations from suberone ; the main points of the chemistry of this group are shown in the scheme on Table XX, page 125.

The method of exhaustive methylation applied by Ladenburg and Merling in their researches on the alkaloids led incidentally to the formation of *cyclo*-heptatriene, and Willstätter[1] unravelled its structure by the methods indicated above. The curious reaction of benzene with diazoacetic ester, discovered by Büchner, will be discussed more fully under the head of the aliphatic diazo compounds.

The *cyclo*öctane hydrocarbons are little known, but the properties of *cyclo*-octatetrene are interesting in relation to those of benzene. Our knowledge of the family derives from two main sources ; firstly, the ring ketone from azelaic acid, *cyclo*octanone obtained in small yield by heating the thorium salt of azelaic acid ; *cyclo*octanone is a pleasant smelling solid, m. 40-41°, b. 195–197°. The second source is the pelletierine group of alkaloids. Methylgranatonine (*ψ*-pelletierine) (92) is a pomegranate alkaloid, and by applying the method of exhaustive methylation it is possible to remove the nitrogenous internal link, leaving the outer shell of eight carbon atoms intact. The degree of unsaturation depends on the starting point and the manipulations subsequent to exhaustive methylation. The various stages and products are shown in the diagram below :—



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[1] Willstätter and Waser, *Ber.*, 1911, **44**, 3423 ; Willstätter and Heidelberger, *Ber.* 1913, **46**, 517.

The b. pts., of the commoner *cyclo*öctane hydrocarbons are given in the table below :—

*cyclo*öctane	150°
*cyclo*öctene	145°
*cyclo*öctadiene-1, 3	135–138°
*cyclo*öctadiene-1, 4	143–144°
*cyclo*öctatriene	147–148°
*cyclo*öctatetraene	36°/14 mm.

It is interesting to note that the boiling points of the aromatic hydrocarbons corresponding to the larger rings are similar. Thus, benzene boils at 80·4° ; *cyclo*hexane at 81° ; toluene at 110° ; *cyclo*heptane at 117° ; the xylenes boil at 138–142°, which is comparable with the figures in the table above.

The properties of *cyclo*öctatraene do not in any way resemble those of benzene, the characteristic aromatic stability of the latter being entirely absent. The tetraene is very unstable, easily isomerises, and shows the utmost readiness to add bromine and to exhibit the normal properties of ethylenic unsaturation. In this connexion, the remarks of Bachman and Hoaglin [1] are worthy of quotation :—

> " The properties of *cyclo*öctatetraene, especially its relative instability and reactivity, are of considerable significance to our theories of the nature of the aromatic nucleus. The continuously conjugated system of double bonds present in benzene may be the cause of the general inertness of that substance. If such conjugation is a sufficient cause of the inactivity, then *cyclo*butadiene and *cyclo*öctatetraene should resemble benzene (*cyclo*-hexatriene) very closely in chemical properties. So far, all attempts to synthesize *cyclo*butadiene have been unsuccessful, but this may or may not mean such a substance, once made, would be unstable and reactive. The burden of proof therefore lies heavily upon *cyclo*öctatetraene. Willstätter's original synthesis of this substance led to a product which was very unstable. This proved so surprising that organic chemists have made sporadic attempts ever since to devise new syntheses for this important compound. Other workers have pointed out the possibility that the compound prepared by Willstätter was not *cyclo*öctatetraene but something else, and many chemists have been reluctant to accept as proven facts the existence and great reactivity of this substance.
>
> " As a matter of fact, the reactivity of a hydrocarbon having the structure of a *cyclo*öctatetraene may be predicted on the basis of the resonance theory. The resonance energy which stabilises benzene (39 k cals/mole) would be greatly reduced in *cyclo*öctatetraene in spite of an increase in the number of double bonds and resonance forms in that substance. This is a result of the fact (as shown clearly by models) that the eight-membered, fully conjugated ring must exist either in a strained or in a puckered form. If the ring is strained, then a considerable portion of the expected resonance energy will be lost in straining the atomic bonds from their normal angles. If the ring is puckered, then atomic motions are necessary to alter the pucker in going from one resonance form to another. Resonance is greatly diminished in non-planar rings of this type due to these atomic movements. Probably the actual form taken by *cyclo*öctatetraene would be a partially puckered, partially strained ring with greatly reduced resonance energy. The low resonance energy would lead to reactivity of the type normally associated with double bonds."

It was at this point that *cyclo*öctatetraene was prepared in enormous industrial quantities by the polymerisation of acetylene in the presence of nickel salts, especially the halides and cyanide.[1] This observation was developed by the German chemical industry during the second world war, and it is most interesting to note that both the original work of Willstätter and the predictions of Bachman and Hoaglin are amply confirmed

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[1] Bachman and Hoaglin, *J. Org. Chem.*, 1943, **8**, 309.

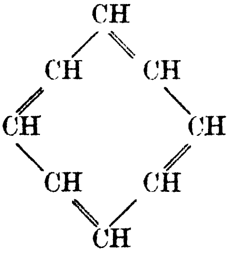
Thus, in the Table XX*a* is shown the properties obtained by modern workers using considerable quantities of material carefully purified from the industrial bulk, and those originally obtained by Willstätter thirty years previously ; the correspondence is remarkable.

TABLE XX*a*

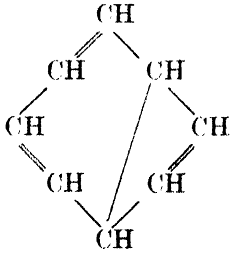
THE PROPERTIES OF *Cyclo*ÖCTATETRAENE

	Recent Work (*cf. Reppe*).	*Older Work* (*cf. Willstätter*).
Boiling point (760 mm.)	142-143°	—
Boiling point (17 mm.)	42·0-42·5°	42·2-42·4°
Melting point	- 7°	- 27°
Density (d_4^0)	0·9382	0·943
Density (d_4^{20})	0·9206	0·925
Refractive index N_D^{20}	1·5290	1·5389
Molecular refraction	35·17	35·2
Molecular exaltation	- 0·09	- 0·12
Dielectric constant	2·74/20	—
Heat of combustion	1069·02 cal.	—
Dipole moment	0·069 × 10^{-18} esu.	—

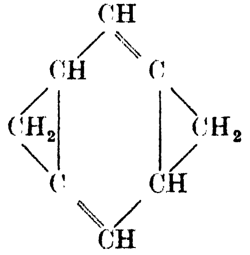
Further, the general chemical properties of *cyclo*öctatetraene are such as to confirm the calculations of Bachman and Hoaglin, since it is much more of an ethylenic hydrocarbon than an aromatic type like benzene. The chemical reactions are extremely interesting, and the substance bids fair to be one of the most important sources of aliphatic and alicyclic chemicals. It is undoubtedly a substance which can react in a variety of forms, the three principal of which are shown below :—



(I)



(II)



(III)

*Cyclo*öctatetraene may be catalytically reduced to *cyclo*öctane or to *cyclo*öctene, the latter being the more useful substance, as it is readily converted to suberic acid, to *cyclo*öctanol, and from the latter to *cyclo*öctanone, and through the oxime to the lactam of caprylic acid. The tetraene is oxidised by benzoyl peroxide to an epoxide (91*a*) and by mercuric sulphate in aqueous media to phenylacetaldehyde (91*b*). Many of these changes are shown in the diagram below :—

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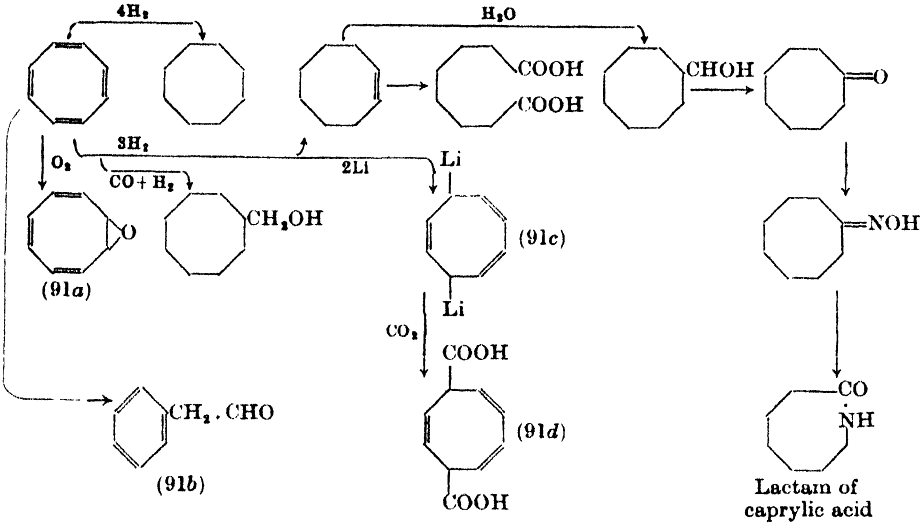
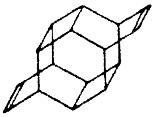
[1] Reppe, *Cyclo*polyolefines, H.M.S.O., London.

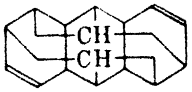


One most important and interesting property of *cyclo*öctatetraene lies in its ability to react with two atoms of lithium, to form the addition product (91*c*), as if the metal had added across the bridge of the formula II. The lithium compound readily gives the dicarboxylic acid of *cyclo*öctatriene (91*d*) with carbon dioxide.

The dimer of *cyclo*öctatetraene is often written as in (91*e*) below, but it is as well to realise that this " cage " form is the exact equivalent of the anthracene structure (92).



(91*e*).



(92).

There are many larger ring compounds known, but as they are mainly ketonic, their chemistry is discussed in an Appendix to Chapter VII. In addition, some mention should be made at this point of the very large number of fused rings which are not only frequently met with in Nature, but which can also be synthesised ; dicyclic hydrocarbons such as pinane and camphane, together with tricyclic substances such as tricyclene (94), their derivatives and those of carane and thujane (mainly alcohols, aldehydes and ketones) are widely distributed in Nature, and form an important section of the terpene family ; a discussion of their chemistry will be found in Chapter VIII.

A peculiar instance of a tricyclic hydrocarbon is that of adamantane, a solid substance obtained from Moravian petroleum.[1] This substance has the same crystal lattice as diamond, and represents one unit of diamond structure hydrogenated. It is a sparkling crystalline (cubic) substance with an odour of camphor, stable to nearly all reagents. The symmetrical arrangement of its atoms leads to a phenomenally high m.p. 268°. Further, the high refractive index (1·568) of adamantane also points to a compact carbon lattice, as in diamond. The conventional plane representation (93) of its formula does not give a true picture of its structure ; the diagram (96) shows it to consist of four *trans cyclohexane* rings, symmetrically disposed ; tricyclene (94) is also better represented by the perspective formula (95). Compounds of this group

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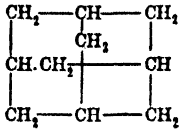
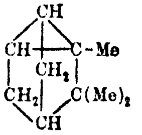
[1] Landa, *Coll. Czechoslov. Chem. Commns.*, 1933, **5**, 1.

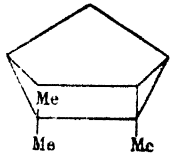


(93)

present a problem in systematic nomenclature. The formal orthodox method is to relate the tricyclic system to the corresponding bicyclic system in the following way :—



(94)



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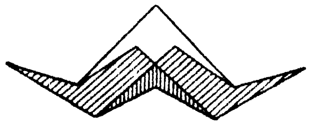

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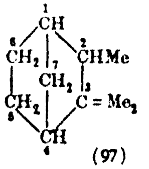
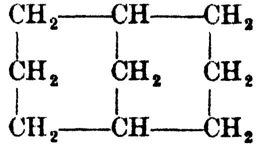


(97)

Tricyclene, $C_{10}H_{16}$

A. The formal method considers the structure (97) as a 2, 3, 3-trimethyl derivative of a bi*cyclo*heptane, and tricyclene as 2, 3, 3-trimethyltricyclo-$[2, 2, 1, 0^{2,6}]$-heptane. The numbers in the square brackets are arrived at by taking the numbers of carbon atoms constituting the three bridges between the common carbon atoms of the bicyclic system (97) followed by the number of carbon atoms in the additional bridge of the tricyclic system using superior affices to indicate the position of the bridge, e.g.

Bi*cyclo*[3, 3, 1]nonane :—



(99)

A. The normal method relates adamantane to the bicyclic hydrocarbon (99) and names it tri*cyclo* (3, 3, 1, $1^{3,7}$) decane.

B. A second, and very convenient method would be to call adamantane 1 : 5, 3 : 7 *bis*-endomethylene*cyclo*öctane.

Aromatic Hydrocarbons

The aromatic hydrocarbons are all derived from the *cyclo*hexatriene (benzene) ring either by substitution, or by the process loosely referred to as the " fusion " of rings, in which two adjacent carbon atoms are shared by two rings. The peculiar properties of benzene and its homologues usually referred to under the term 'aromatic' include a remarkable stability and chemical resistance, and the almost entire absence of the additive properties usually associated with ethylenic unsaturation. Ease of substitutive reactions such as halogenation, nitration and sulphonation is another characteristic 'aromatic' property. The whole question of the physico-chemical implications of aromatic character is discussed in Vol. III.

The detection of naphthalene in coal-tar by Garden in 1819, and the isolation of the pure substance by Kidd in 1820, was the first discovery of an aromatic coal-tar hydrocarbon. The subsequent discovery by Faraday in 1825 of the benzene in illuminating gas obtained from the pyrolysis of fish oils led him to investigate a number of similar hydrocarbons, including the naphthalene of Kidd, to which in 1826 he gave the correct empirical formula allowing, of course, for the atomic weight of carbon accepted at that time; he did not, however, connect benzene with naphthalene or with coal-tar. The study of benzene rested here until 1834, when Mitscherlich obtained benzene ('benzin' was his version) by distilling benzoic acid with quicklime. The problem of nomenclature now became acute; Faraday had termed his hydrocarbon 'bicarburet of hydrogen' and Laurent in 1835 suggested the name now universally adopted, 'benzene'; he also suggested an alternative name 'phène' which was never adopted except by a small French-speaking minority. Laurent's second name, however, gave rise to the name 'phenyl' for the radicle C_6H_5, and is perpetuated in a multitude of compound names. Two years after Mitscherlich's isolation of benzene from benzoic acid the indefatigable Pelletier and his assistant Walter isolated toluene from the destructive distillation of pine resin. Later, in 1841, Deville obtained it from Tolu balsam.

It remained for A. W. Hofmann in 1845 to obtain benzene from coal-tar and in 1849 Mansfield obtained toluene from the same source. Meanwhile, in 1832, Dumas and Laurent had isolated anthracene from coal-tar. It is, therefore, a remarkable fact that of the three common hydrocarbons in coal-tar, naphthalene and anthracene were isolated long before benzene was recognised as a constituent.

Coal-tar is one of the main sources of benzene, but much benzene is obtained by scrubbing coal and coke-oven gas with high boiling oils. Coal-tar contains about a hundred compounds, mostly aromatic, of which about thirty are extracted industrially. Considerable quantities of aromatic hydrocarbons are also to be found in petroleum from certain districts, notably Borneo and Galicia; benzene is not the main constituent, toluene and xylenes preponderating. Thus in a Byoritsu crude from Formosa the first run distilling up to 155° showed 3 per cent. benzene, and 20 per cent. each of toluene and xylene. Mesitylene and higher homologues of benzene were also present in small quantities. Such crudes constitute the main source of industrial toluene and xylene.

We owe to Kekulé[1] the recognition of the cyclic nature of the benzene structure, and, through his discovery, of cyclic structure in general. Prior to 1865, when Kekulé announced his theory, there had been recognised only acyclic compounds. This simple conception of Kekulé is a keystone to the arch of organic chemistry, and the remarks of M. Bert[2] express this elegantly :—

> " La chimie organique est attirée de plus en plus vers la biochimie et la chimiothérapie ; tant que le mystère et le danger de la tuberculose et du cancer, pour ne citer que ces deux maux redoutables, continueront à peser sur la pensée humaine, nombres de chercheurs poursuivront sans répit

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[1] Kekulé, *Bull. Soc. Chim.*, 1865, **3**, 98; Liebig's *Annalen*, 1866, **137**, 129.
[2] Bert, " Traité de Chimie Organique " [Ed. v. Grignard], Vol. IV, p. 6.

vitamines et remedès specifiques. Or, une bonne formule de constitution pour une substance-mère est le plus puissant facteur de succès ; quelle preuve plus convaincante que les quelque deux cent mille composès issus de l'hexagone de Kekulé ? La crainte de voir perdre de son efficace le merveilleux outil que a créé les industries organiques suffrait, à elle seule, à tenir en éveil l'esprit critique des inventeurs."

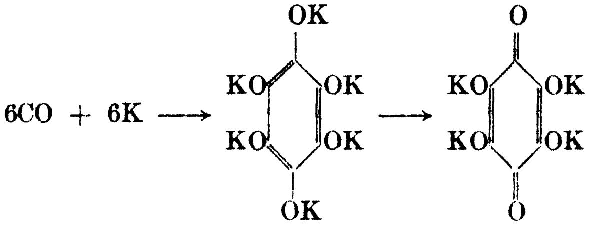
Before considering in detail the properties of the individual hydrocarbons of the series it is proposed to discuss the various methods of conversion of aliphatic to aromatic compounds, and vice versa. It is convenient to divide the reactions into groups according to the number of molecules involved in the synthesis 6, 4, 3, 2 or 1. It is not, of course, suggested that where a number of molecules is involved the synthesis is not progressive or stepwise ; the division of these reactions into groups has no other significance than convenience.

Six Molecule Syntheses

(1) Methane gives benzene under pyrogenic conditions.[1]

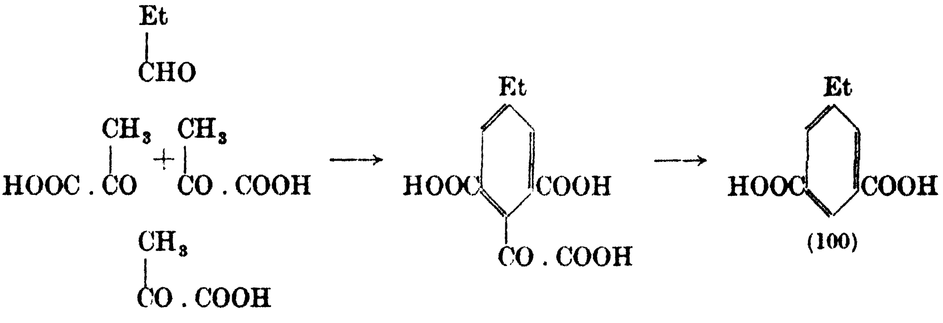
(2) Carbon tetrachloride under similar conditions gives hexachlorobenzene.[2]

(3) Carbon monoxide and potassium yield six-ring compounds, first the potassium derivative of hexahydroxybenzene, and by acidification, the salts of rhodizonic acid and tetrahydroxyquinone :—



Four Molecule Syntheses

(4) Three molecules of pyruvic acid[3] and one of propanal give *s*-ethyl isophthalic acid (100).



(100)

(5) Four molecules of pyruvic acid[4] can be converted to uvitic acid (101) by the following changes :—

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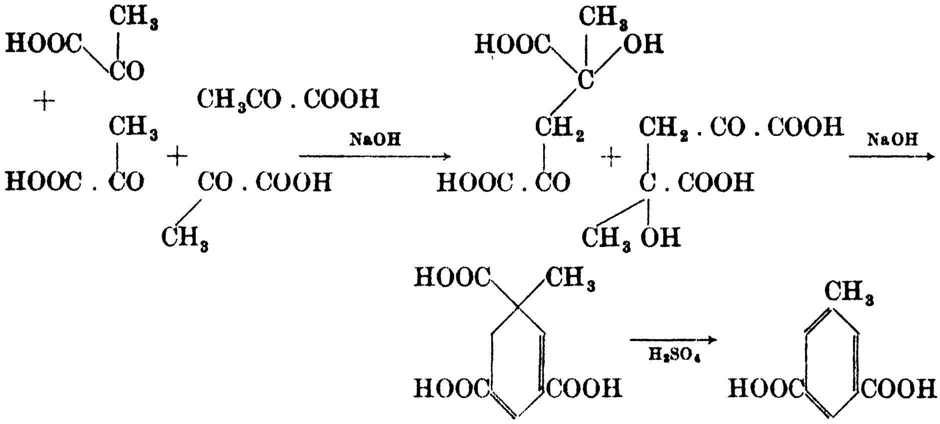
[1] Berthelot, *Ann. Chim. Phys.*, 1863, **67**, 59.
[2] Schall, *Chem. Zentr.*, 1909, **1**, 717.
[3] Dobner, *Ber.*, 1890, **23**, 2379 ; 1891, **24**, 1746.
[4] Wolff *et al.*, *Ann.*, 1860, **113**, 358.



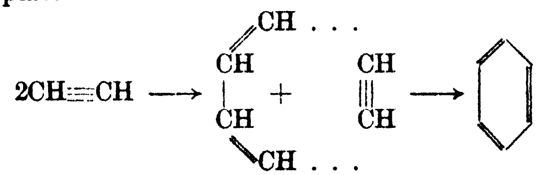
(101)

Three Molecule Syntheses

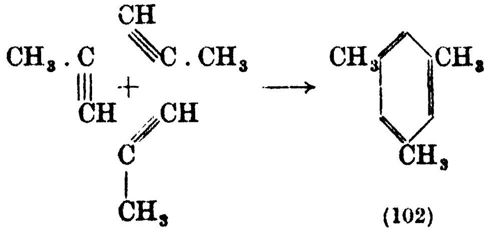
There are many examples where three molecules of a simple structure combine, probably always in two stages, to form a benzenoid derivative. As early as 1866 Berthelot[1] showed that three molecules of acetylene combined, at least to some extent, to form benzene. The reaction, written

$$3CH{\equiv}CH \longrightarrow C_6H_6$$

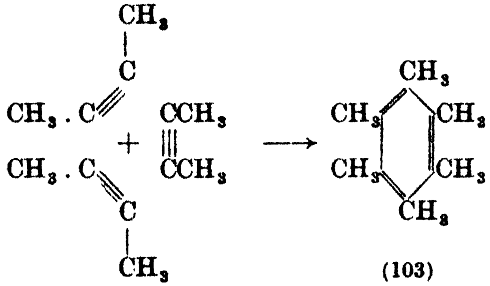
probably takes place



The reaction is general and substituted acetylenes polymerise quite readily to give trialkylbenzenes ; thus propyne gives mesitylene[2] (102) and butyne-2 gives hexamethylbenzene[3] (103)



(102)



(103)

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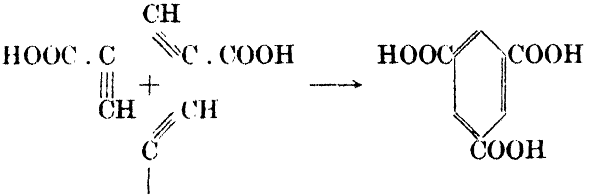
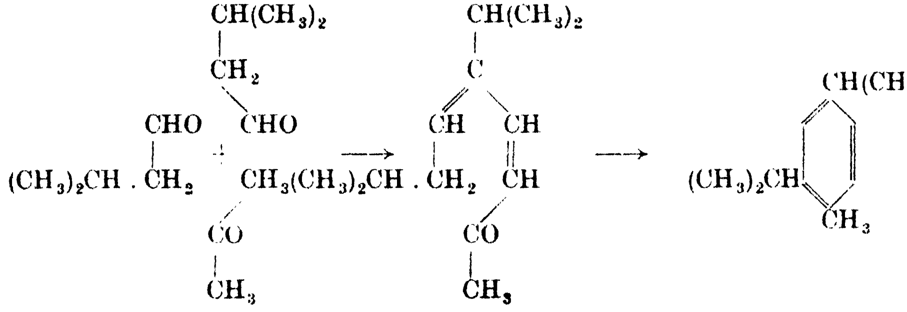
[1] Berthelot, *Bull. Soc. Chim.*, 1866, **9**, 446.
[2] Fittig and Schrohe, *Ber.*, 1875, **8**, 17 ; 367.
[3] Aldedingen, *J. Soc. Phys. Chem. Russ.*, 1881, **13**, 392.

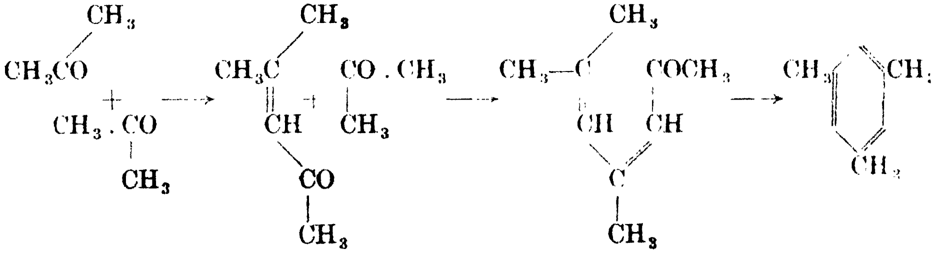
The reaction persists with halogenated acetylenes (e.g., bromoäcetylene gives *s*-tribrombenzene in sulphuric acid suspension [1]) and with propiolic acid which gives trimesic acid (104) [2]



(104)



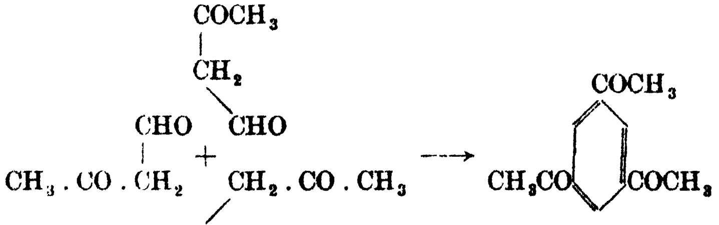
(105) (106)



(107) (108) (109)

A general reaction of considerable value in building up aromatic nuclei is based on the tendency which ketones show [3] to condensation between successive molecules. Thus, acetone gives mesityl oxide (107), and finally mesitylene (109) under the influence of dehydrating agents. In the same way, butanone gives *s*-triethylbenzene [4] and pentanone, tripropylbenzene.

A variation of the previous method is to allow a molecule of acetone to condense with two of *iso*valeraldehyde (3-methylbutanal) when 2, 4-di-iso-propyl toluene (106) is obtained. The intermediate stage (105) can be isolated. Exactly analogous is the condensation of three molecules of butanalone-3 to give 2-triacetylbenzene (110) [5]



(110)

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[1] Sabaniev, *J. Soc. Phys.-chem. Russ.*, 1885, **17**, 176.

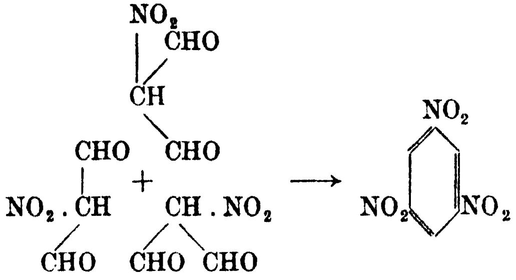
[2] Baeyer, *Ber.*, 1886, **19**, 2185.

[3] Kane, *J. Pr. Chem.*, 1835–1839, **15**, 131 ; Fittig and Bruckner, *Ann.*, 1868, **147**, 42.

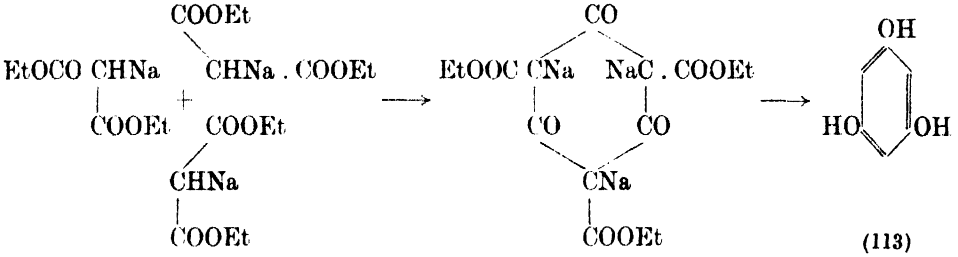
[4] Jacobsen, *Ber.*, 1874, **7**, 1435.

[5] Claisen and Stylos, *ibid.*, 1888, **21**, 1145.

The aldehydes and half-aldehydes of the malonic series are fertile subjects for condensation to benzene derivatives. Thus, nitromalonic aldehyde (2-nitropropandial) (111)[1] gives *s*-trinitrobenzene (112) :—

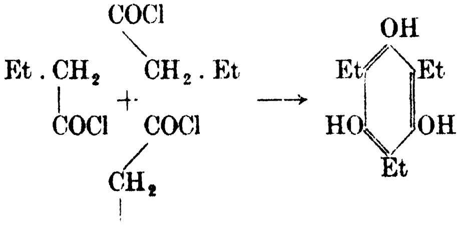


(111) (112)



(113)

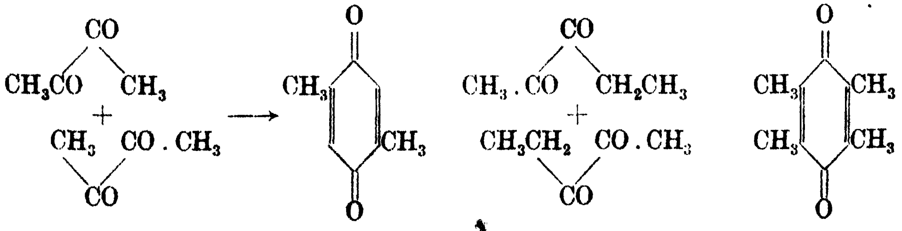
whilst one molecule of sodio-nitromalodialdehyde and one of acetone give *p*-nitrophenol. The fusion of sodiomalonic ester with caustic potash gives phloroglucinol (113), through a number of intermediate stages.[2] Triethylphloroglucinol (114) is obtained by the condensation of three molecules of butyryl chloride in the presence of anhydrous aluminium chloride[3]



(114)

Two Molecule Syntheses

These, although fewer in number than the three molecule syntheses, comprise some interesting transformations, e.g., two molecules of diacetyl readily condense to give *p*-xyloquinone (115).[4] The reaction is a general one for simple α-diketones ; thus, two molecules of pentandione-2, 3 give one of duroquinone (116).



(115) (116)

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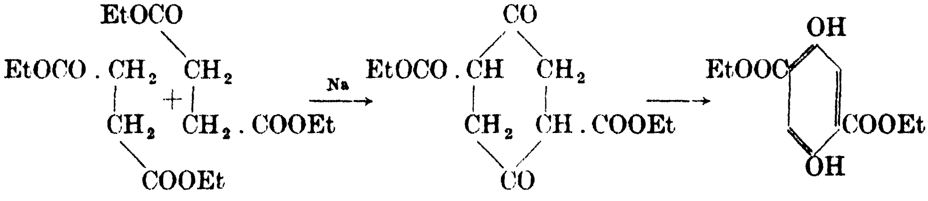
[1] Hill and Torray, *Ber.*, 1895, **28**, 2597.

[2] Baeyer, *ibid.*, 1885, **18**, 3458.

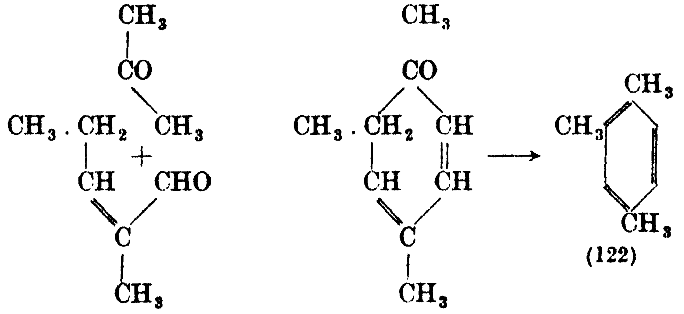
[3] Coombes, *Ann. Chim. Phys.*, 1887, **12**, 263.

[4] Pechmann, *Ber.*, 1888, **21**, 1420.

Other examples in this class are the condensation of two molecules of succinic ester (117) in the presence of sodium, which induces ring formation to the structure (118). This readily loses hydrogen when treated with bromine,



(117) (118) (119)

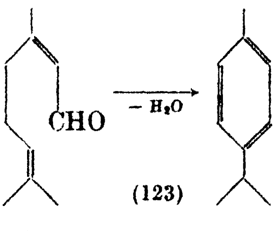


(120) (121) (122)

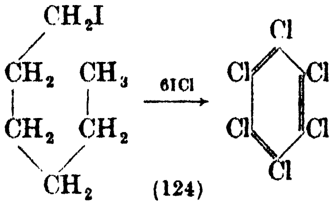
giving dihydroxyterephthalic ester (119).[1] A somewhat similar instance is the condensation of acetone and 2-methyl-pentenal-2 (120) with acetone to give ψ-cumene (122) *via* the intermediate (121).[2]

Single Molecule Syntheses

It will have been realised that many of the previous syntheses of aromatic rings from two or more molecules often involve as a final stage the single molecule syntheses, i.e., ring closure without increase in the number of carbon atoms. The examples given below are of aromatic ring formation from substances in which the six carbons essential to the nucleus are already present. Many such examples are met with in terpene chemistry (q.v.), and only one example is given here, the direct conversion of citral (123) to *p*-cymene by warming with potassium hydrogen sulphate.[3]



(123)



(124)

Hexyl iodide is converted to hexachlorobenzene by the action of iodine monochloride (124).[4] Into this group also falls Willstätter's stepwise conversion of cyclohexanone (from calcium pimelate) to benzene,[5] the course of which is sufficiently indicated by the formulæ below :—

---

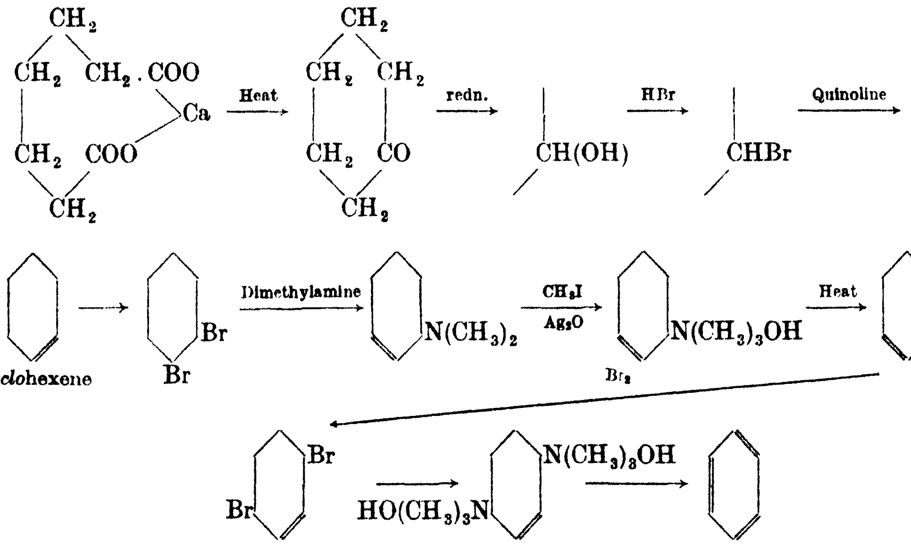
[1] Herrmann, *Ann.*, 1882, **211**, 309, 327, 335.

[2] Jacobsen, *Ber.*, 1877, **10**, 856.

[3] Dodge, *Am. Chem. J.*, 1890, **12**, 561 ; Semmler, *Ber.*, 1891, **24**, 204.

[4] Krafft, *Ber.*, 1876, **9**, 1085.

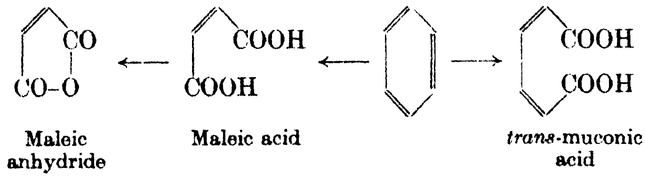
[5] Willstätter.



This series of reactions, with its progressive introduction of successive double bonds, lends considerable support to the Kekulé conception of the aromatic ring (see also Vol. III). Much information on this type of synthesis is given in Goose's book (see Appendix).

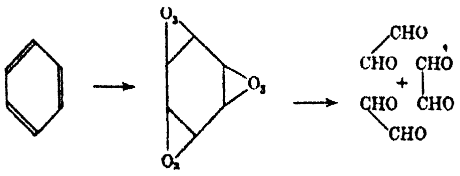
Aromatic-aliphatic Conversions

Benzene may be oxidised with air in the presence of a catalyst to give maleic anhydride—a reaction which is used as the basis for the industrial production of maleic acid; biologically, the ingestion of benzene in mammalia leads to its excretion, in part at least, as *trans*-muconic acid[1] (m. 298°; a white, microcrystalline substance) (125):—



(125)

Ozone gives with benzene a triozonide which decomposes to glyoxal,[2] a reaction which has also been used in arguments to prove that the Kekulé structure has a real existence. The action of ozone on *o*-xylene is, however, much more interesting as the three compounds obtained, glyoxal, methylglyoxal and diacetyl could only be obtained by the breakdown of two isomeric ortho-compounds,[3] as indicated in (126) (see also Vol. III). An unusual reaction leading to the breakdown of benzene to aliphatic compounds is the action of



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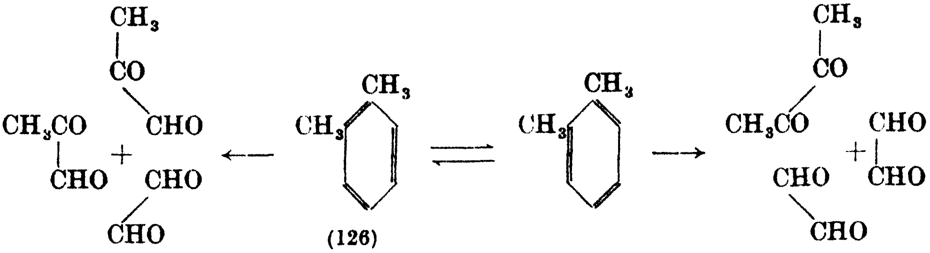
[1] Jaffé, *Z. Physiol. Chem.*, 1909, **62**, 58.

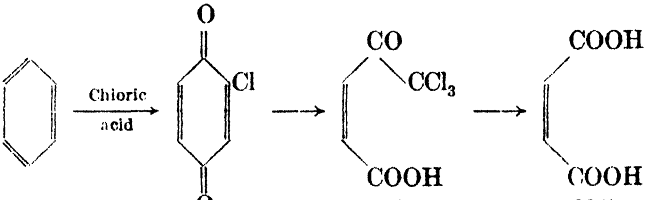
[2] Harries and Weiss, *Ber.*, 1904, **37**, 3431.

[3] Levine and Cole, *J.A.C.S.*, 1932, **54**, 338.

chloric acid. The first product is chloro-quinone, the ring of which is then opened and converted to 1, 1, 1-trichloropentene-3-one-2-acid-5 (127) and finally to maleic acid (128).[1]

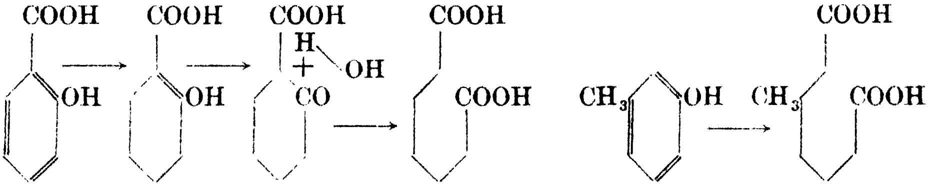


(126)



(127) (128)

Many phenolic compounds are converted to aliphatic substances by energetic reduction with sodium and alcohol. Thus, salicylic acid gives pimelic acid (129); indeed, the reduction of the analogous cresotinic acids is the only convenient method of obtaining the methylpimelic acids (130).

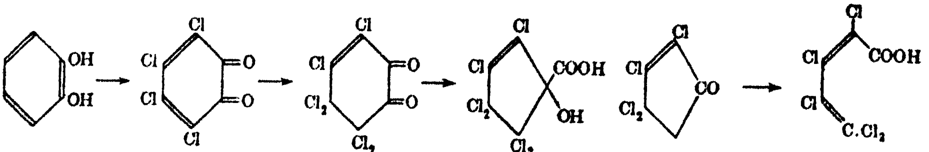


Pimelic acid (129) Methylpimelic acid (130)

Nearly all hydroxybenzene derivatives are oxidised to chlorinated aliphatic derivatives when treated with chlorine under suitable conditions; the familiar formation of chloropicrin, $CCl_3 . NO_2$ from picric acid and chlorine in the presence of line is one example, others are :—

(1) Phenol[2] to trichloropyruvic acid, $CCl_3 .CO . COOH$ by sodium chlorate and hydrochloric acid.

(2) Catechol[3] to 2, 3, 4, 5, 5 pentachloropentadiene-2, 4-acid-1 (131).



(131)

(3) Hydroquinone[4] to dichloromaleic acid (132) and trichloroethylene (133).

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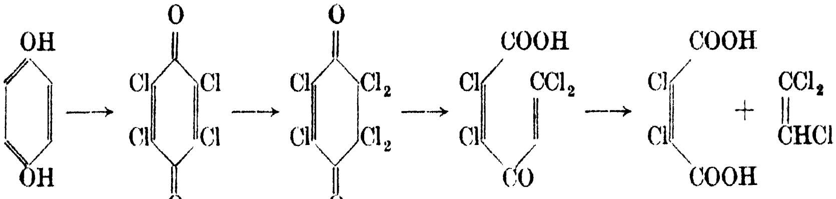
[1] Kekulé and Strecker, *Ann.*, 1884, **223**, 175.

[2] Einhorn and Willstätter, *ibid.*, 1895, **286**, 257.

[3] Zincke, *Ber.*, 1894, **27**, 3364.

[4] Zincke, *Ann.*, 1892, **267**, 1.


(132) (133)

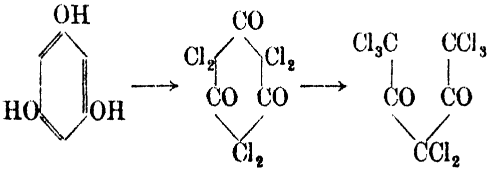
(4) Resorcinol[1] gives a variety of products, amongst which are the following:

(*a*) Dichloromaleic acid (2, 3-dichlorobutene-2-diacid-1, 4).

(*b*) Pentachloroglutaric acid (2, 2, 3, 4, 4-pentachloropentane-diacid-1, 5).

(*c*) 1, 1, 5-Trichloropentene-4, dione-2, 3.

(5) Phloroglucinol[2] is converted by chlorination to octachloroacetylacetone (134).


(134)

INDIVIDUAL AROMATIC HYDROCARBONS

The physical properties of some of the members of this series are shown in the table below :—

TABLE XXI

Formula	Hydrocarbon	M.P.	B.P.	Specific gravity		Refractive index	
				t	S.G.	t	n_D
C_6H_6	Benzene	+ 5·493°	80·2°	20/4°	0·874	15°	1·504
$C_6H_5CH_3$	Toluene	— 95·7°	110·8°	15/4°	0·8716	8·5°	1·50349
$C_6H_4(CH_3)_2$	1, 2 Xylene	— 29°	143·9°	20/4°	0·8812	20°	1·5050
$C_6H_4(CH_3)_2$	1, 3 Xylene	— 54°	138·8°	15/4°	0·8686	8·4°	1·50324
$C_6H_4(CH_3)_2$	1, 4 Xylene	+ 13°	135·5°	20/4°	0·8611	23·4°	1·4942
$C_6H_5 . C_2H_5$	Ethylbenzene	— 92·8°	188·5°	15/4°	0·872	8·4°	1·50206
$C_6H_3(CH_3)_3$	1, 2, 3 Hemimellitene	—	175·5°	19·6/4°	0·8949	19·5°	1·513
$C_6H_3(CH_3)_3$	1, 2, 4 Cumene	— 57·4°	168·2°	20/4°	0·8764	15·3°	1·507
$C_6H_3(CH_3)_3$	1, 3, 5 Mesitylene	— 57·5°	164·5°	4/4°	0·8768	14·6°	1·4966
$C_6H_4(CH_3)Et$	1, 2 Methylethylbenzene	—	164·8°	15·7/4°	0·8841	15·7°	1·506
$C_6H_4(CH_3)Et$	1, 3 Methylethylbenzene	—	161·5°	17·9/4°	0·8690	17·9	1·498
$C_6H_4(CH_3)Et$	1, 4 Methylethylbenzene	—	162·5°	14/4°	0·8690	14°	1·494
$C_6H_2(CH_3)_4$	1, 2, 3, 4 Prehnitene	—	203°	16/4°	0·9044	16°	1·520
$C_6H_2(CH_3)_4$	1, 2, 3, 5 Isodurene	—	197°	16/4°	0·8961	—	—
$C_6H_2(CH_3)_4$	1, 2, 4, 5 Durene	79°	195°	81/4°	0·8380	81°	1·47896
$C_6H_4(C_2H_5)_2$	1, 2 Diethylbenzene	—	184°	15·7/4°	0·8770	15·7°	1·501
$C_6H_4(C_2H_5)_2$	1, 3 Diethylbenzene	—	181°	16/4°	0·863	—	—
$C_6H_4(C_2H_5)_2$	1, 4 Diethylbenzene	— 35°	182°	15/4°	0·8682	15°	1·497
$C_6H_4(CH_3)(C(CH_3)_2)$	*p*-Cymene	— 73·5°	177·3°	20/4°	0·862	13·7°	1·4926
$C_6H(CH_3)_5$	Pentamethylbenzene	53°	231°	107/4°	0·8472	107·5°	1·48484
$C_6(CH_3)_6$	Hexamethylbenzene	164°	265°	—	—	—	—

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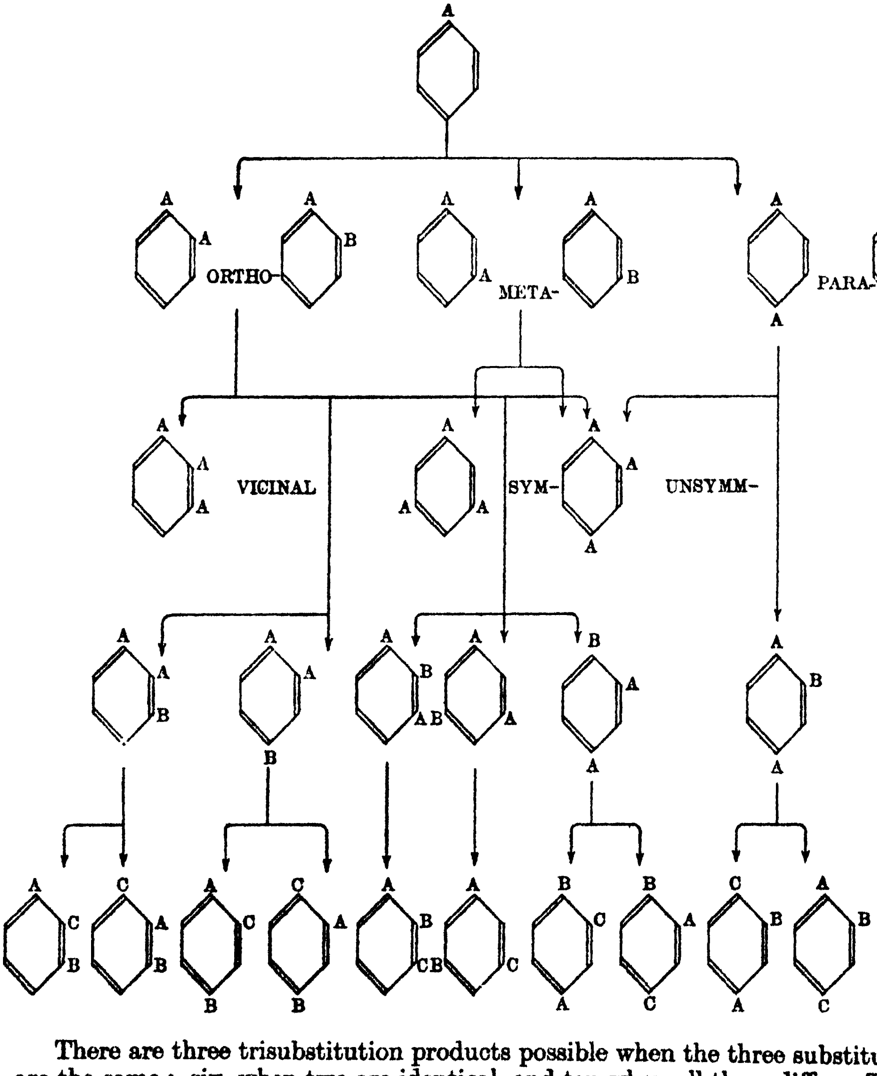
[1] Zincke and Rabinowitch, *Ber.*, 1890, **23**, 377.

[2] Zincke and Kegel, *ibid.*, 1890, **23**, 1706.

Isomerism in the Benzene Series

There is no doubt that the immediate appeal of the ring conception was its ability to account satisfactorily for the phenomena of isomerism shown amongst benzene derivatives. Thus, there is only one mono substitution product, e.g., mononitro-, monochloro- or mono-methyl derivative, and the higher substituted derivatives agree in number and orientation exactly with those predicted from Kekulé's hypothesis. There are only three disubstitution products, whether the two substituting groups are the same or not :—

TABLE XXII



There are three trisubstitution products possible when the three substituents are the same ; six, when two are identical, and ten when all three differ. These orientations are shown in Table XXII. The various arrangements of four and five substituents in the benzene ring are shown in Tables XXIV and XXV ; there are three tetrasubstituted benzenes possible when all four substituents are the same ; the number of possible structures increases rapidly, and in some cases the examples are too numerous to illustrate. The number of possible isomers is given in Table XXIII.

Naturally, the number of possible arrangements of substituents increases sharply with the condensed nuclei, naphthalene, anthracene and phenanthrene, where the structure is, unlike benzene, a source of asymmetry; with phenanthrene there are over twelve hundred derivatives with substituents A_2BC, and the possibilities with nine different substituents are nearly half a million. Very few of these highly substituted derivatives are met with amongst either natural or synthetic products.

TABLE XXIII

BENZENE DERIVATIVES

Substituents	*Isomeric Forms*	*Substituents*	*Isomeric Forms*
A	1	A_2B_2C	16
A_2	3	A_2BCD	30
AB	3	ABCDE	58
A_3	3	A_6	1
A_2B	6	A_5B	1
ABC	10	A_4B_2	3
A_4	3	A_4BC	3
A_3B	6	A_3B_3	3
A_2B_2	11	A_3B_2C	6
A_2BC	16	A_3BCD	10
ABCD	30	$A_2B_2C_2$	11
A_5	1	A_2B_2CD	16
A_4B	3	A_2BCDE	29
A_3B_2	6	ABCDEF	58
A_3BC	10		

SOME INDIVIDUAL MEMBERS OF THE AROMATIC SERIES

Benzene, C_6H_6.—Reference has already been made to the polymerisation of acetylene to benzene, discovered by Berthelot. There is some evidence that this may ultimately be developed as a method for the production of industrial benzene. Iki and Ogura [1] obtained up to 70 per cent. conversion of ethylene to liquid polymers by using active charcoal at 650–660°, approximately half the yield being benzene. There is seldom any necessity for the laboratory preparation of benzene; the methods which can be used for its preparation are shown diagrammatically at the top of p. 144. The production from benzoic acid, aniline or salicylic acid could be carried out from natural materials other than coal (gum benzoin, indigo and oil of wintergreen) so that the benzene obtained would be free of all traces of thiophen. On the other hand, coal-tar benzene from the persistent fractionation of light oil can be obtained almost free from all other substances, except thiophen, which may be removed by violent agitation with mercurous acetate solutions, a procedure which mercurates the thiophen to α-thienyl mercuri-acetate, a substance which remains in the aqueous phase.

Benzene is a colourless limpid liquid m. 5·493° b. 80·2°. Benzene dissolves about 0·2 per cent. of water at ordinary temperatures, a determination which was carried out by an interesting application of the silver perchlorate method.[2]

Benzene forms a number of double compounds with aluminium chloride and bromide, of the general formula $[C_6H_6]_nAlR_3$, orange substances, which were discovered during Gustavson's investigation of the Friedel and Craft's reaction. Benzene forms an interesting complex with ammonia and nickel cyanide, which

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[1] Iki and Ogura, *J. Chem. Ind. Japan*, 1927, **30**, 461.
[2] Hill, *J.A.C.S.*, 1923, **45**, 1143.

TABLE XXIV

Some Tetra-substituted Benzene Structures

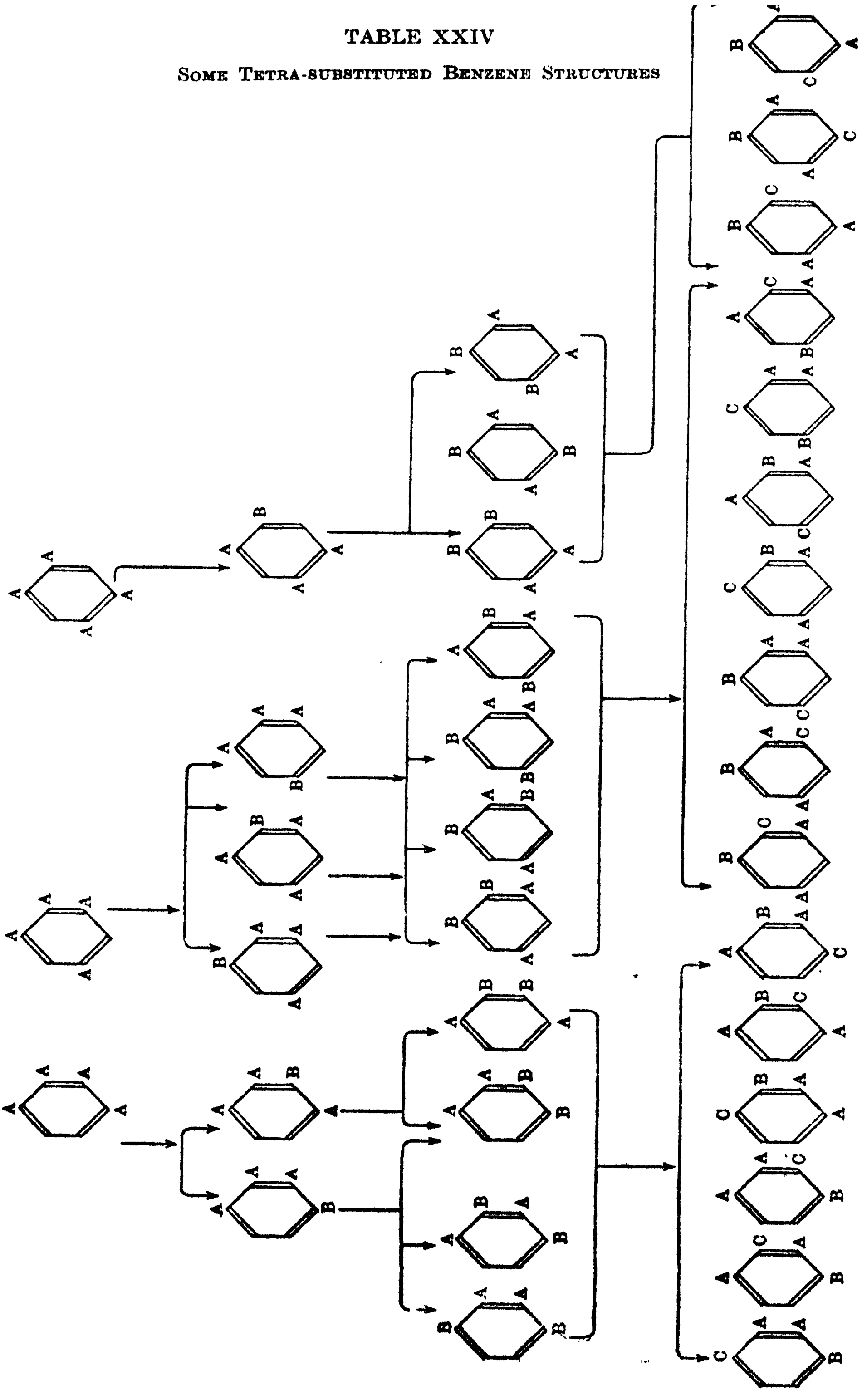
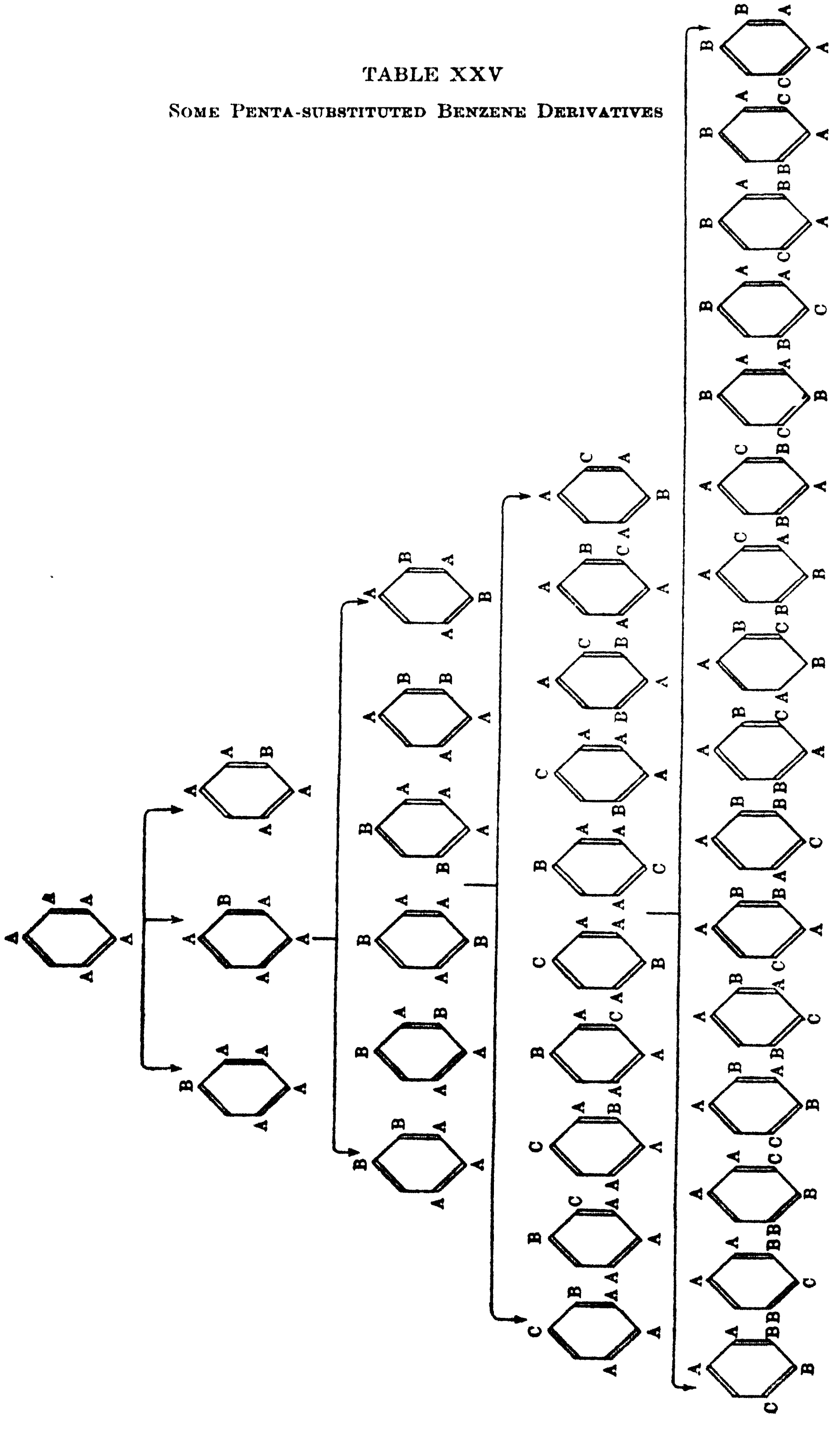
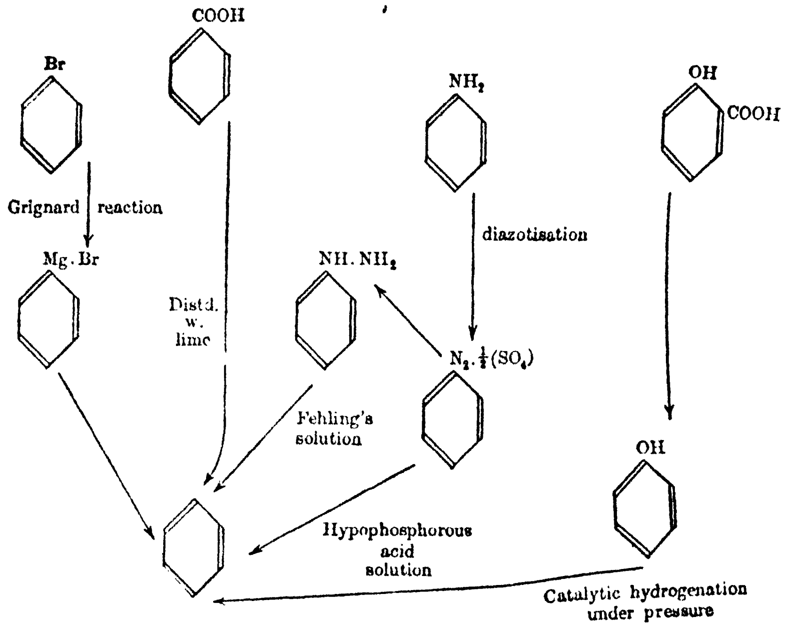


TABLE XXV

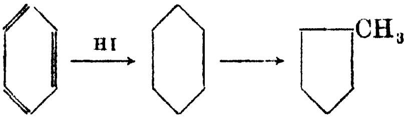
Some Penta-substituted Benzene Derivatives





is used for the estimation of benzene in gas analysis. The general reactions of benzene may be summarised as follows :—

(1) *Reduction.*—Benzene is reduced by strong (D, 1·8) hydriodic acid with the formation of both *cyclo*hexane and methyl *cyclo*pentane (135) showing that



(135)

under conditions of the experiment an extrusion has taken place. Using Sabatier's method *cyclo*hexane alone is obtained, albeit not so readily as the methyl and dimethyl analogues are obtained from toluene and xylene.

(2) *Oxidation.*—The oxidation of benzene to maleic acid by the action of chloric acid has already been discussed ; maleic anhydride may more readily be obtained from benzene by oxidising its vapour in the presence of air and of a vanadium catalyst, a method which has acquired industrial significance. Direct oxidation of benzene in the electrolytic cell has been recorded ; the end-product being benzoquinone.[1]

(3) *Thermal Decomposition.*—When benzene vapour is heated, the reaction $2C_6H_6 \longrightarrow C_6H_5—C_6H_5 + H_2$ takes place ; Berthelot's original experiments on this reaction were carried out by conducting the vapour through red hot tubes, but this has been replaced on a large scale by passing the vapour through melted lead to which a little sodium has been added, the latter acting as a catalyst. Small quantities of terphenyl $C_6H_5 . C_6H_4 . C_6H_5$, *s*-triphenylbenzene, and *p*, *p*′-diphenyl diphenyl (didiphenyl) are also produced at the same time.

(4) *Action of Halogens on Benzene.*—Pure benzene in the absence of the usual chlorine carrying catalysts, and in the presence of light yields the addition product, hexachloro*cyclo*hexane (α-form, m. 157°). Ethylene appears to

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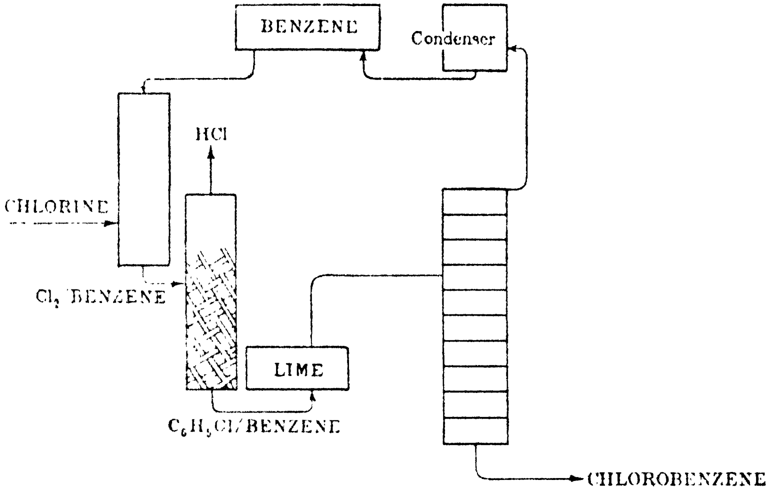
[1] Ch. Claudius, *Rev. Prod. chim.*, 1918, **21**, 219.

catalyse the addition reaction,[1] but the more usual chlorine-carrying catalysts lead to substitution. Industrially, iron is used as a catalyst, as it enables a high yield of monochlorobenzene to be obtained; such catalysts as iodine and phosphorus halides lead to a mixture of higher chlorinated derivatives. Aronheim[2] first pointed out the abnormal behaviour of molybdenum pentachloride as a catalyst in the chlorination of benzene. The presence of 1 per cent. of the pentachloride in anhydrous benzene leads to rapid and smooth chlorination to *p*-dichlorobenzene which can be isolated in substantial amount from the product.

Industrially, benzene is chlorinated either by a batch process in the presence of iron, or continuously. The batch process is quite simple to operate, iron being used as the catalyst. In the continuous process benzene is run down a column against a rising stream of dry chlorine; solution takes place and the benzene-chlorine solution passes through a cooled reaction tube, where it meets a cooled mass of iron borings; reaction takes place, hydrogen chloride being evolved and a solution of crude chlorobenzene in benzene passing from the bottom of the column, where it is neutralised with lime and passes to a stripping column.



This is a simple bubble-cap tower, with steam-heated coils on the lower plates. The chlorobenzene is led off from the bottom and benzene vapour from the top. The latter is, of course, condensed and re-cycled.

Bromine reacts with benzene more sluggishly than does chlorine, although analogous products are obtained. In sunlight, and in the absence of moisture, a hexabromo addition product is obtained. In the presence of iron, monobromo- and *p*-dibromobenzene are formed; with iodine as catalyst, higher substitution products may be produced. The reaction has been investigated in detail by Bruner.[3] Benzene is almost unacted upon by iodine, and fluorine converts it to carbon tetrafluoride. In the presence of its higher oxidation products, however, iodine is capable of converting benzene to iodo derivatives; iodic acid, periodic acid, or even iodine and nitric acid together convert benzene to a mixture of iodobenzene and *p*-diiodobenzene.

Much discussion has centred round the mechanism of halogenation of benzene, chiefly as to whether addition precedes substitution; the general conclusion is that it does, and that the stages in chlorination are best expressed :

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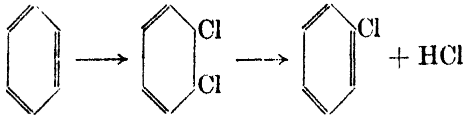
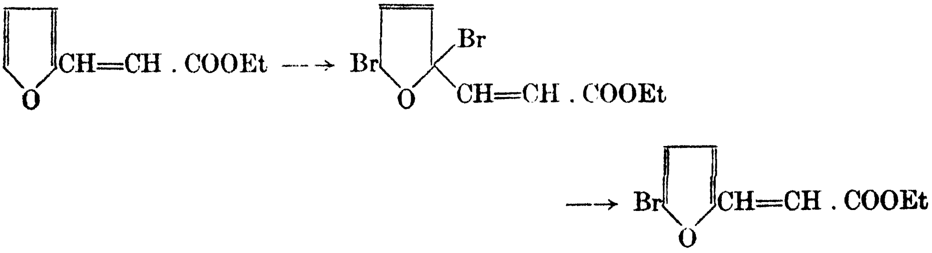
[1] Stewart and Hanson, *J.A.C.S.*, 1931, **53**, 1121.
[2] Aronheim, *Ber.*, 1875, **8**, 1400.
[3] Bruner, *Z. Phys. Chem.*, 1902, **41**, 513.



Gilman [1] has shown that in the somewhat analogous case of the bromination of furylacrylic ester (1, 4 epoxyheptatriene-1, 3, 5-acid-7, ethyl ester) a dibromo-addition product may be isolated :—



(5) *Nitration.*—Ease of nitration distinguishes aromatic from aliphatic hydrocarbons. Benzene, nitrated with a mixture of nitric and sulphuric acids under suitable conditions is almost wholly converted to mono-nitrobenzene. It is almost certain that addition precedes the loss of water ; v. Alphen [2] was able in the case of 4, 4′-dimethoxydiphenyl to isolate the addition product—which is blue in colour ; on contact with sulphuric acid this nitrobody passes into 3, 3′-dinitro-4, 4′-dimethoxydiphenyl.

The use of stronger acids and higher temperatures converts benzene almost entirely into *m*-dinitrobenzene, a little *o*- and *p*-dinitro compounds being produced at the same time ; under very rigorous conditions *s*-trinitrobenzene may be obtained by direct nitration, but the yield is small, and tri-nitration of benzene is only attained with difficulty.

(6) *Sulphonation.*—Ease of sulphonation is also an attribute of aromatic character ; benzene is readily sulphonated to the monosulphonic acid ; with oleum, a second sulphonic group is introduced, the isomers being *m*- and *p*-benzene disulphonic acids ; no *ortho* isomer has been isolated from this reaction. Under the most energetic conditions, benzene yields trisulphonic acids, the 1, 3, 5-isomer always predominating, and it is doubtful whether a fourth sulphonic group can be directly introduced into benzene.

Toluene.—Toluene was discovered by Pelletier and Walter in 1837,[3] and also isolated from Tolu balsam by St. Claire Deville in 1841.[4] Some toluene is still produced from coal-tar, although most is obtained from the petroleum fractions mentioned on page 131. Constitutional syntheses such as the Würtz reaction lead to some toluene and Gilman and others[5] have shown that the sequence of reactions is probably :—

$$\begin{aligned} C_6H_5Br + 2Na &\longrightarrow C_6H_5Na + NaBr \\ C_6H_5Na + BrCH_3 &\longrightarrow C_6H_5CH_3 + NaBr \end{aligned}$$

This is based on the observations (*a*) that bromobenzene parts more readily from its halogen than does methyl bromide, and (*b*) that sodium phenyl does not react readily with further bromobenzene, but reacts with the methyl halide preferentially. This accounts for the large predominance of toluene over ethane and diphenyl in the reaction-product ; a similar reaction has been used for the experimental production of ethylbenzene. The formation of alkali metal derivatives of the aromatic hydrocarbons, in reactions of this and other types, was suspected long before there was definite proof of their existence. In 1936, Gilman conducted numerous experiments on the interaction of potassium ethyl and benzene, and was able to demonstrate the existence not only of potassium phenyl, but also of *p*-phenylene dipotassium :—

---

[1] Gilman, Brown and Dickey, *Proc. Iowa. Acad. Sci.*, 1929, **36**, 265.
[2] van Alphen, *Rec. Trav. Chim.*, 1930, **49**, 153.
[3] Pelletier and Walter, *Ann. Chim. Phys.*, 1837, **67**, 269.
[4] St. Claire Deville, *ibid.*, 1841, **3**, 168.
[5] Gilman, Paceirtz and Baine, *J.A.C.S.*, 1940, **62**, 1514.

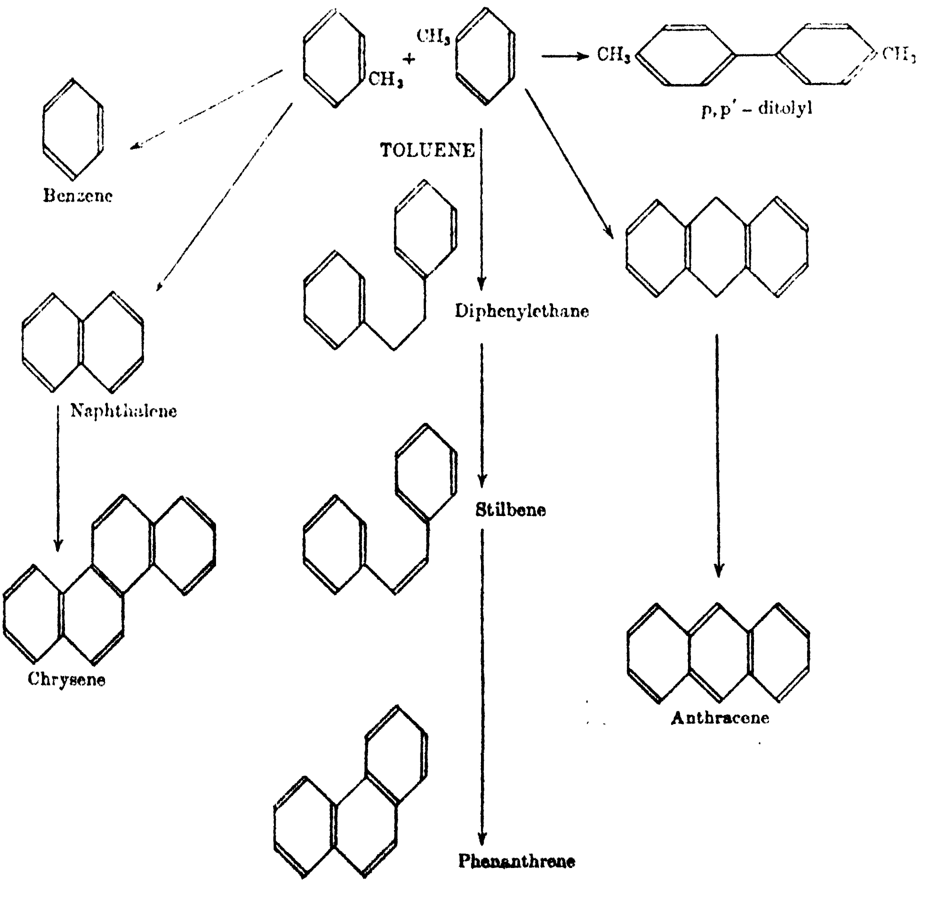
$$C_6H_6 + KC_2H_5 \longrightarrow C_6H_5K + C_2H_6$$
$$C_6H_6 + 2KC_2H_5 \longrightarrow C_6H_4K_2 + 2C_2H_6$$

The volatility of ethane facilitated the separation of the product, and the existence of the two potassium derivatives was demonstrated by the action of carbon dioxide :—

$$C_6H_5K + CO_2 \longrightarrow C_6H_5COOK$$
$$C_6H_4K_2 + 2CO_2 \longrightarrow C_6H_4(COOK)_2$$

Considerable quantities of benzoic and terephthalic acids were isolated, together with recognisable traces of phthalic acid, indicating that substitution follows the general rule, the para-isomer predominating.

Naturally, the chemistry of toluene differs from that of benzene, in that the methyl group offers a second point for attack by reagents and a distinction is made between *nuclear* and *side-chain* reactions. Thus, the pyrolytic decompositions of toluene are much more complex than those of benzene ; loss of hydrogen from the side-chains leads to diphenylethane and stilbene and the course of these reactions is summarised in the scheme below :—



The mechanism of the formation of benzene, naphthalene and chrysene is not clear, but the presence of members of the phenanthrene and anthracene series might be anticipated.

An unusual reaction of toluene is that with nitrosyl chloride, with which at 10° and in sunlight it gives quite good yields of ω-nitrosotoluene, $C_6H_5.CH_2NO$. Compared with benzene, toluene is much easier to reduce, oxidise, chlorinate or nitrate, the methyl group acting as a point of attack. A case in point is the interaction of toluene and sulphur at 190–230° when stilbene is produced :—

$$C_6H_5 . CH_3 + 2S \longrightarrow C_6H_5 . CH{=}CH . C_6H_5 + 2H_2S$$

Benzene is not attacked under similar conditions. Reduction of toluene is most easily secured by Sabatier's method, and, as with benzene, the ring is reduced by hot, concentrated hydriodic acid with some extrusion to dimethyl*cyclo*pentane.

Toluene shows considerable tendency to react with acetic acid with the formation of benzyl alcohol. Thus, in glacial acetic acid at 120°, it gives benzyl alcohol and acetaldehyde,[1] and the same end product is produced by a variety of oxidants—including oxygen itself—in the presence of U.V. light, especially in the presence of carriers such as anthraquinone.[2]

The oxidation of toluene has been the subject of considerable study, with a view to obtaining benzaldehyde. With the ordinary reagents of the laboratory —chromates and permanganates, the end product is benzoic acid, and considerable difficulty is experienced in stopping the reduction at an earlier stage. Oxidation with atmospheric air in the presence of vanadium or molybdenum catalysts has been attempted with some success ; but it is almost impossible to avoid the formation of some benzoic acid, and the physical conditions of the oxidation must be controlled within very narrow limits in order to prevent complete oxidation. A process was operated industrially for some time in which manganese mud and sulphuric acid in the presence of a copper salt were used, but considerable quantities of benzoic acid were unavoidably formed. Étard's method of oxidation with chromyl chloride, usually in carbon disulphide solution, has been recommended for the laboratory oxidations of alkyl benzenes, since its progress stops short after the oxidation to aldehyde, but the explosive nature of the intermediates formed and its cost render it unsuitable for industrial use. Reference has already been made to the sulphur oxidation of toluene to stilbene ; the analogous oxidation with potassium persulphate yields dibenzyl. Toluene may be oxidised to benzaldehyde by cerium dioxide in sulphuric acid solution.[3]

The presence of the side-chain of toluene makes its halogenation complex ; in light, especially ultra-violet light, and in the presence of chlorine carriers such as phosphorus halides, chlorine gives side-chain substitution almost exclusively, and over 90 per cent. conversion to benzyl chloride can be obtained. In the dark, however, and with moist chlorine, nuclear substitution can be induced up to at least 80 per cent. The *ortho-* and *para*-chlorotoluenes are produced in almost equal amounts, the *ortho*-isomer being slightly in excess ; some 2, 4-dichlorotoluene is also obtained.

The sulphonation of toluene is also more readily accomplished than that of benzene, a mixture of *o-* and *p*-toluene sulphonic acids being obtained (see also Appendix II, Chap. X). Nitration of toluene proceeds quite easily, mixtures of the *o-*, *m-* and *p*-mononitro compounds being obtained. The *ortho*-compound preponderates being present to 60 per cent. ; 36 per cent. of the *para*-compound is obtained, with 4 per cent. of the *meta-*. These figures are obtained in a straightforward nitration, using mixed acids ; by using acetyl nitrate (see

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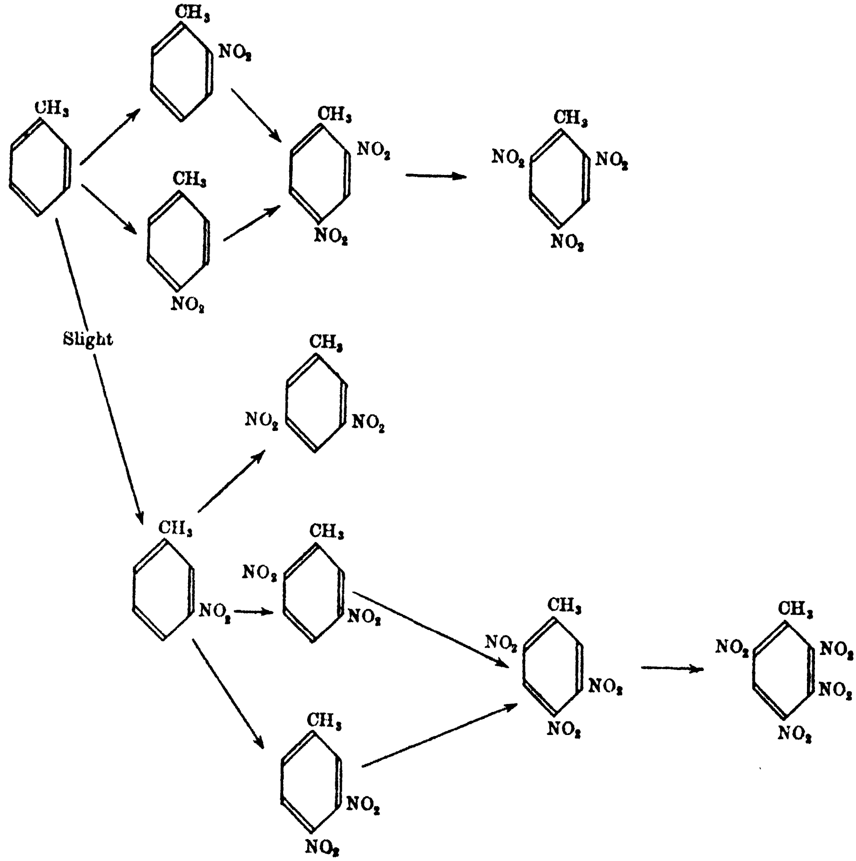
[1] Giacolone, *Gazz. Chim. Ital.*, 1931, **61**, 828.

[2] Kothari and Watson, *J. Ind. Inst. Sci.*, 1931, **44**, 11.

[3] D.R.P. 158609, *J.S.C.I.*, **51**, 1930, 159.

Vol. II, Chap. I) the proportion of *ortho-* and *meta-* forms may be increased. Nitration to 2, 4-dinitrotoluene is easily accomplished, and the 2, 4, 6-trinitro compound is also readily obtained ; four nitro groups can only be introduced when the first goes into the *m*-position, as in the scheme below :—



The Xylenes.—Cahours, in 1850, first isolated xylene from coal-tar. The three xylenes are found together in coal-tar and in certain types of petroleum, whilst *m*-xylene is frequently obtained with benzene and toluene during pyrolytic treatment of simple alkyl hydrocarbons. In coal-tar xylene, the proportions of isomers are approximately *ortho-* 10 per cent. ; *meta-* 70 per cent. ; *para-* 20 per cent. In petroleum, proportions vary, but Tauss[1] has given the following figures for the C_8 aromatic fraction of petroleum from various sources :

TABLE XXVI

Source	Xylenes			Ethylbenzene
	o-	*m-*	*p-*	
Roumania .	24	42	17	16
California .	20	56	8	16
Italy . .	9	77	5	9
Borneo .	10	62	12	16
Pennsylvania	36	47	4	13

[1] Tauss, *Z. Angew. Chem.*, 1919, **32**, 361.

The use of fractionation on a large scale with suitably designed columns will separate the *ortho*-xylene (b. 143·9°) from the *m*- and *p*-isomers (b. 138·8° and 138·5° respectively). The *ortho*-xylene may be purified by treatment with cold concentrated sulphuric acid. If the sulphuric acid layer be removed and worked up for sodium *o*-xylene sulphonate, this may be recrystallised and any *m*-sulphonate will remain behind in the mother liquors, being more soluble. On treatment of the *meta*-*para*-fraction with sulphuric acid, the *meta*-isomer dissolves, leaving the *para*- unaffected. In this way comparatively pure products may be obtained, and an adequate separation effected. The sulphuric acid method has also been used on the mixed isomers prior to fractionation, but the separation is tedious, as it involves the fractional crystallisation of the mixed sodium salts of *ortho*- and *meta*-xylene sulphonic acids. Clark and Taylor [1] give a critical discussion of the various methods of separation, none of which are entirely satisfactory. Much xylene is used industrially as the mixture of isomers boiling 137–145°, separation being necessary only when required for specific products such as musk substitute and Vitamin B_2.

In general there is a parallel between the chemical behaviour of the xylenes and that of toluene, since both have opportunities for nuclear and side-chain reactivity. Oxidation proceeds most easily with *ortho*-xylene, least easily with *para*-xylene. The nitration of *ortho*- and *meta*-xylene is quite normal, and follows the scheme outlined below, tending to proceed in the case of the *ortho*-compound to the 4, 5-dinitro compound, and with the *meta*-isomer to the symmetrical trinitro derivative. On the other hand, *para*-xylene gives only a single mononitro compound which leads to a mixture of the 2, 3 and 2, 6 dinitro compounds on further nitration ; only traces of 2, 5 compound are formed.

Industrially there are few specific uses for *o*- and *p*-xylenes ; the *m*-isomer is valued for conversion to its xylidine (4-amino-1, 3 dimethyl benzene) used in dyestuffs manufacture and for the manufacture of xylene musk.

Ethylbenzene and propylbenzene (b.p. 135·17° and 157° respectively) are hydrocarbons which are being produced in considerable quantity by the interaction of ethylene and propylene with benzene in the presence of anhydrous aluminium chloride ; so far their potentialities as starting points for organic synthesis have not been fully explored.

Of the three trimethylbenzenes, pseudocumene and mesitylene are available in experimental quantities, but the vicinal member hemimellitene is a great rarity and has only been occasionally isolated. Pseudocumene can readily be isolated from the 160–170° fraction of coal-tar, or more profitably from the corresponding fraction from the product of allowing four molecular proportions of methyl chloride to react with benzene in the presence of anhydrous aluminium chloride. If this fraction is warmed with [2] sulphuric acid at about 90°, cooled and treated with water equal in volume to one-third of the acid used, the pseudocumene sulphonic acid remains dissolved in the oily layer which, on removal and treatment with a further quantity of water and the whole cooled and allowed to stand, deposits pseudocumene sulphonic acid. This may be separated, purified by recrystallisation, and reconverted to pseudocumene by heating with hydrochloric acid.

Hemimellitene, the vicinal trimethylbenzene, has been obtained from the 172–180° fraction of the materials mentioned in the previous paragraph. By careful fractionation of about 40 litres of crude material, using a 2-metres insulated packed column and a high reflux ratio, about 8 litres of a fraction, boiling 174–177°, can be obtained which contains most of the hemimellitene. This is sulphonated and the liquor diluted until a crop of mixed hydrocarbon

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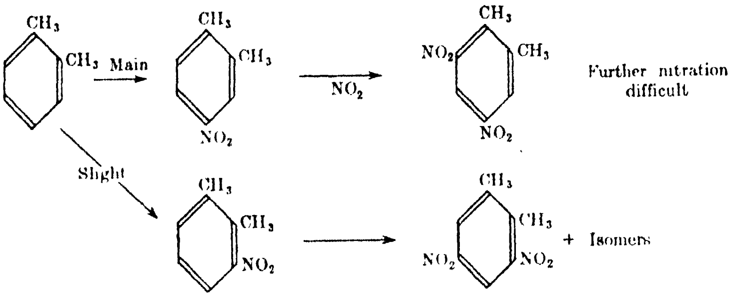
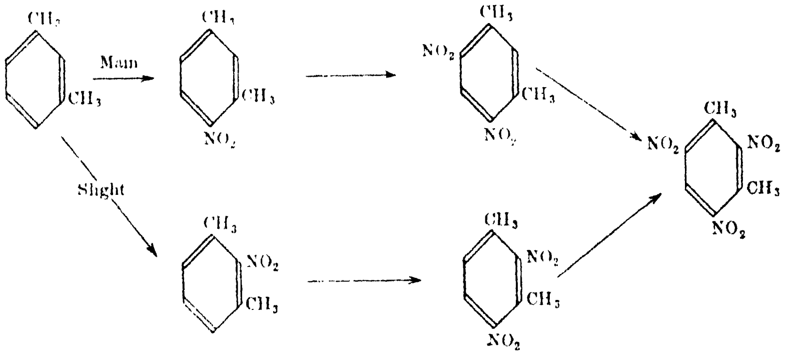
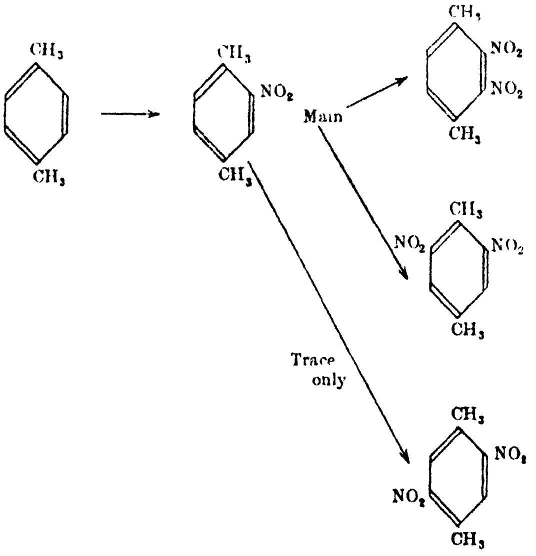
[1] Clark and Taylor, *J.A.C.S.*, 1923, **45**, 830.

[2] Jacobsen, *Ber.*, **14**, 2628 ; *Ann.*, 1876, **184**, 199.





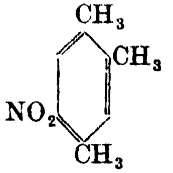


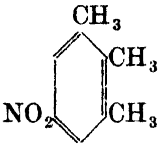
sulphonic acids separates. These are converted to the sulphonamides (*via* the barium and sodium salts) and by fractional crystallisation hemimellitene sulphonamide (m. 195°) is separated from pseudocumene sulphonamide (m. 181°). Distillation of the former with concentrated hydrochloric acid regenerates the hydrocarbon.

The preparation of mesitylene is usually carried out in the laboratory by the dehydration of acetone, working details of the process being given in 'Organic Syntheses' (Coll. Vol. I) (see also p. 131).

The most reactive of the three trimethylbenzenes is undoubtedly mesitylene, from which it is not easy to obtain a monochloro or mononitro derivative without some di- or tri-substituted analogues being formed at the same time. Chlorination tends to produce trichloromesitylene (m. 204–205°) in long lustrous needles, and nitration proceeds almost entirely in the first instance to dinitromesitylene, a magnificant substance crystallising in prisms often 3 cm. in length.[1]

Nitration of pseudocumene and hemimellitene is more normal, but much ω-nitro isomer is also produced. In the case of pseudocumene the substituent group, whether nitro or otherwise, almost invariably enters the "5" position; the same is true of hemimellitene :—

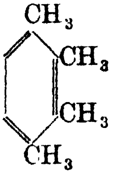




The 5-nitropseudocumene and 5-nitrohemimellitene are readily reducible to amines. No industrial application of the hydrocarbons or their derivatives has so far been developed, and of the whole group pseudocumidine is the only member appearing in trade lists.

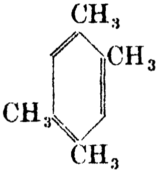
The Tetramethylbenzenes

The formulæ of the three tetramethylbenzenes are shown below :—



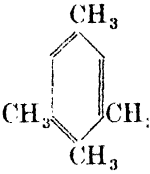
1, 2, 3, 4 Tetramethylbenzene

Prehnitene



1, 2, 4, 5 Tetramethylbenzene

Durene



1, 2, 3, 5 Tetramethylbenzene

Isodurene

Durene is the member of this series most commonly met with, and was first prepared by Fittig and Jannasch[2] in 1870, by the interaction of bromopseudocumene and methyl iodide in the presence of sodium. It is readily prepared by the action of methyl chloride on benzene in the presence of anhydrous aluminium chloride. After the reaction product has been decomposed with water, the oily layer is extracted with benzene, dried and fractionated ; on cooling, the fraction distilling at 188–194° crystallises, is drained and recrystallised from alcohol. Durene forms large crystals, m.p. 80°, b.p. 191–192°, and received its name because it was the first solid hydrocarbon to be discovered in the benzene series. Isodurene may be obtained from the drainings of crude durene in the fraction mentioned above; by diluting the liquid portion somewhat with petroleum ether and chilling to — 35° most of the durene separates ; on pouring off the supernatant liquid and fractionating, isodurene, b. 195° may be obtained.

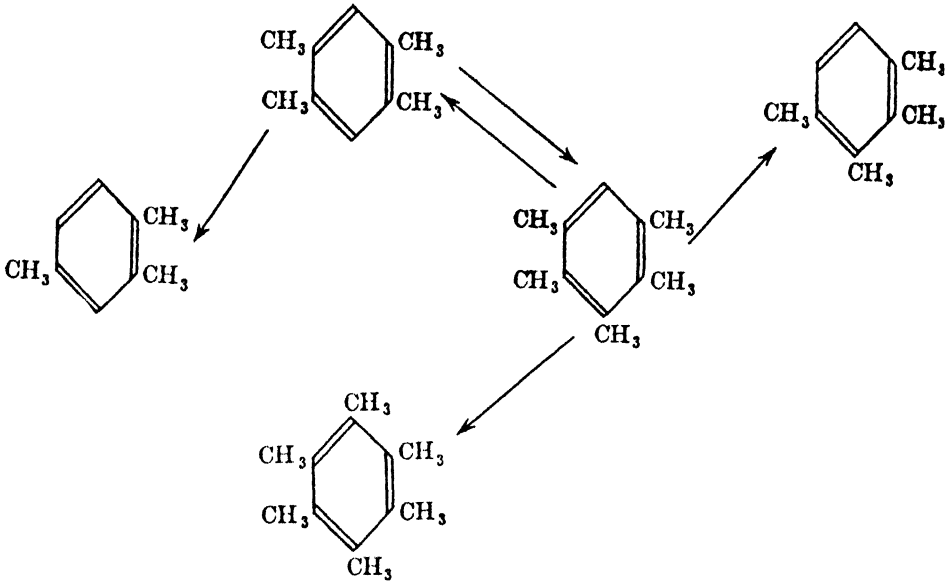
Prehnitene, or vicinal tetramethylbenzene, is a rarity, and we owe much of our knowledge of it to the observation of Jacobsen[3] of a curious disproportionating reaction. When durene is treated with sulphuric acid, some hexamethylbenzene is formed, together with pseudocumene, which is sulphonated, giving a mixture of isomeric pseudocumene sulphonic acids. At the same time, a fair quantity of prehnitene sulphonic acid is formed. The mechanism of the reaction is obscure, but since Jacobsen observed a similar reaction with pentamethyl benzene the sequence of reactions is probably :—

---

[1] Fittig, *Ann.*, 1869, **151**, 132.

[2] Fittig and Jannasch, *Zeit. Chem.*, 1870, 161.

[3] Jacobsen, *Ber.*, 1886, **19**, 1209 ; 1887, **20**, 900.



If the mixture of sulphonic acids is crystallised and converted to the sulphonamides, the prehnitene sulphonamide is less soluble than the others, and may be separated by fractional crystallisation. It is converted to the hydrocarbon by heating with concentrated hydrochloric acid.

The hydrocarbons are not yet of practical importance, nor are pentamethyl- and hexamethyl benzenes (m. 54°, b. 231° and m. 164°, b. 265° respectively), which are readily obtained by the persistent action of methyl chloride on benzene in the presence of anhydrous aluminium chloride.[1]

Hexamethylbenzene is singular in that it is obtained in small quantities under circumstances where its presence would not be expected, as, for example, when methanol and acetone vapours pass over heated alumina,[2] or by heating phenol and methanol under pressure.[3] A further example is the formation of hexamethylbenzene from trioxymethylene and *cyclo*hexane in the presence of anhydrous aluminium chloride.[4] Hexamethylbenzene, having no hydrogen atoms left in the aromatic ring, is resistant to many reagents, e.g., it cannot be nitrated or sulphonated, but permanganate oxidation gives mellitic (benzene hexacarboxylic) acid.

There are many other alkyl substituted benzenes known ; thus, nearly all the possible ethylbenzenes are known ; isopropylbenzene (cumene) and the methyl isopropylbenzenes (cymenes) are well-known, and are the parent hydrocarbons of the terpene series under which heading their chemistry will be discussed.

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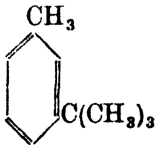
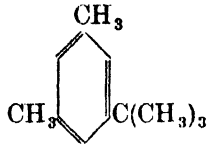
[1] Smith and Dobrovolny, *J.A.C.S.*, 1926, **48**, 1413.
[2] Reckleben and Schreiber, *Ber.*, 1913, **46**, 2363.
[3] Briner, Plüss and Paillard, *H. Chim. Acta.*, 1924, **7**, 1046.
[4] Nastjukoff and Gavin, *Ch. Zentr.*, 1916, **1**, 700.

The two hydrocarbons (136) and (137) 3, *t*-butyltoluene and 5, *t*-butyl-*m*-xylene are valuable as the source of artificial musk (see Vol. II, Chap. I, Appendix II).



(136)

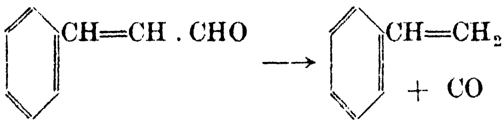


(137)

AROMATIC HYDROCARBONS WITH UNSATURATED SIDE-CHAINS

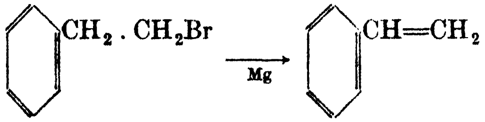
Styrene, or phenyl ethylene, $C_6H_5CH{=}CH_2$, is at present the most industrially important member of the series. Originally discovered by Bonastre[1] in copaiba balsam, it was later found in various other resinous exudations, including styrax and Peruvian balsam, and in the products of dry distillation of dragon's blood. It is also present in coal-gas, to which it gives much of the disagreeable odour associated with that commodity. It is also produced in certain biochemical processes, as when strains of *Aspergillus* and *Pencillium* are grown in media containing cinnamic acid.[2] Numerous experimental procedures have been worked out for obtaining styrene in experimental quantities, the more important of which are summarised below :—

(1) Catalytic decomposition of cinnamic aldehyde in the presence of nickel[3] :—

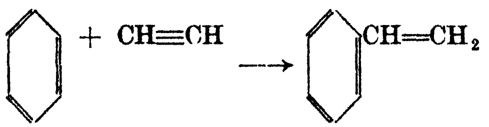


(2) Sabetay's method,[4] the dehydration of phenylethyl alcohol by coarsely powdered caustic potash. Styrene slowly distils over at 140–160°, is decanted from resin, dried over sodium, and rectified over a little hydroquinone. Fourneau[5] modified this method by using a mineral dehydrating agent—porosite.

(3) Ethylbenzene is brominated to give the ω-bromo compound which is then treated with magnesium in dry ether.[6]



(4) Acetylene and benzene, in the presence of anhydrous aluminium chloride, give an 80 per cent. yield of styrene.[7]



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[1] Bonastre, *J. Pharm. Chem.*, 1831, **17**, 341.

[2] Oliviero, *Ch. Zentr.*, 1906, **2**, 608.

[3] Mailhe, *Bull. Soc. Chim.*, 1926, **39**, 922.

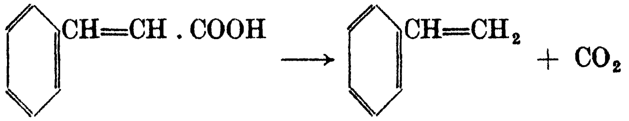
[4] Sabetay, *ibid.*, 1929, **45**, 72.

[5] Fourneau and Puyal, *ibid.*, 1922, **31**, 424.

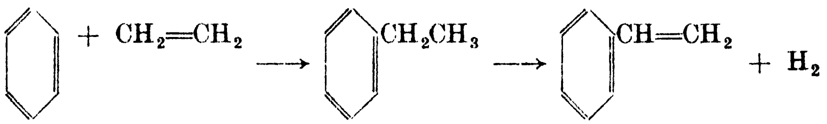
[6] v. Braun and Moldaenke, *Ber.*, 1921, **54**, 618.

[7] Varet and Vienne, *Bull. Soc. Chim.*, 1887, **47**, 918.

(5) For the rapid preparation of small quantities of styrene for laboratory experiments the method of 'Organic Syntheses' is recommended, namely dry distillation of cinnamic acid in the presence of a trace of hydroquinone.



Technically, the large quantities of styrene required for the plastics and synthelast industries are obtained by the condensation of benzene and ethylene in the presence of anhydrous aluminium chloride to give ethylbenzene, which is catalytically cracked to styrene and hydrogen :—



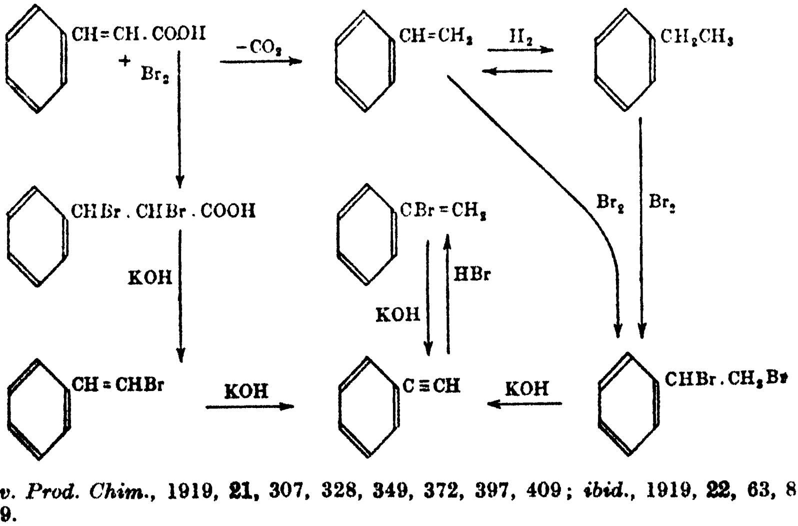
The polymerisation of styrene to *m*-styrene takes place on standing, or on heating and is discussed in Appendix II to this chapter. In glacial acetic acid a dimer is formed :—

$$2\,.\,C_6H_5CH{=}CH_2 \longrightarrow \underset{\text{1, 3-diphenyl-2-methyl propene}}{C_6H_5CH{=}C(CH_3)CH_2C_6H_5}$$

Styrene nitrates abnormally giving ω-nitrostyrene, but reacts normally with hydrobromic acid giving the ω-bromo derivative. A review of much of the chemistry of this hydrocarbon is contained in a series of eleven contributions by Chazel.[1]

There are about eighty aromatic hydrocarbons with unsaturated side-chains ; of these the four described on page 156 are of general interest.

Phenylacetylene (*Phenylethyne*) is a representative of a small group of acetylenic-aromatic hydrocarbons. No simple direct synthesis from acetylene and benzene has been described capable of giving good yields of the substance which is usually obtained by manipulations on the two or three carbon side-chain. Some of these methods are indicated in the diagram below :—



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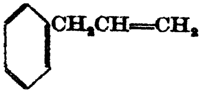
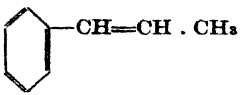
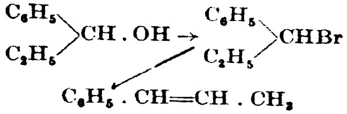
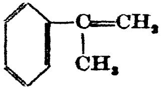
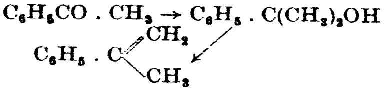
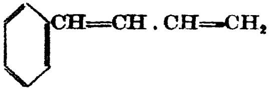
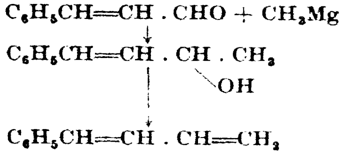
[1] *Rev. Prod. Chim.*, 1919, **21**, 307, 328, 349, 372, 397, 409; *ibid.*, 1919, **22**, 63, 89, 177, 201, 599.

TABLE XXVII

Structure	Name	Preparation	Properties
	1-Phenylpropene-2 (allylbenzene) b. 156–157° $[d]_{0°} = 0{\cdot}907$ $[n]_D = 1{\cdot}5143$	(1) Heating phenyl magnesium bromide with allyl bromide [1] $C_6H_5.MgBr + CH_2{=}CH.CH_2Br \rightarrow C_6H_5CH_2.CH{=}CH_2 + MgBr_2$	A powerfully smelling liquid, showing a strong tendency to pass, on heating, especially in the presence of alkalies, into propenylbenzene
	1-Phenylpropene-1 (propenylbenzene) b. 176° $[d]_{0°} = 0{\cdot}936$ $[n]_D^{20°} = 1{\cdot}5492$	(1) From allylbenzene (see above) (2) From phenylethyl carbinol with conc. HBr., followed by alcoholic KOH 	A strong smelling liquid polymerising readily, and existing in *cis* and *trans* forms
	2-Phenylpropene (Methyl styrene) b. 165° $[d]_{0°} = 0{\cdot}9278$ $[n]_D^{21°} = 1{\cdot}533$	Prepared by Tiffeneau by the action of methyl magnesium iodide on acetophenone followed by dehydration with acetic anhydride 	A liquid which easily polymerises to a crystalline dimer, m. 52°
	1-Phenylbutadiene b_{11} 86° m. 4·5° $[d]_{4°}^{15°} = 0{\cdot}933$ $[n]_D^{16°} = 1{\cdot}6089$	Prepared by reacting methyl magnesium iodide [2] and cinnamic aldehyde, and decomposing the product with ice water 	A substance studied in considerable detail by Muskat and co-workers [3] who has shown it to add reagents almost exclusively in the '-3, 4-' positions, e.g., chlorine gives the 3, 4-dichloro compound

---

[1] Tiffeneau, *C.R.*, 1904, **139**, 482.

[2] Tissier and Grignard, *ibid.*, 1901, **132**, 685.

[3] Muskat and Huggins, *J.A.C.S.*, 1929, **51**, 2496; *ibid.*, 1934, **56**, 1239. Muskat and Grimsby, *J.A.C.S.*, 1930, **52**, 1574. Muskat and Knapp, *Ber.*, 1931, **64B**, 779. Hessler, Muskat and Hermann, *J.A.C.S.*, 1931, **53**, 252.

The most convenient method for laboratory work[1] is to drop ω-bromostyrene onto fused potash. Phenylacetylene is a colourless liquid, b.p. 142–143°, with an unpleasant smell reminiscent of leeks. It has the general properties of an acetylene giving addition compounds and a mono-sodium derivative, which reacts readily[2] with alkyl iodides to give higher analogues, e.g. :—

$$C_6H_5C{\equiv}C\,.\,Na + I\,.\,C_3H_7 \longrightarrow \underset{\text{1-Phenylpentyne-1}}{C_6H_5C{\equiv}C\,.\,(CH_2)_2\,.\,CH_3}$$

An interesting reaction of phenylethyne is with ketones in the presence of potash, the addition giving tertiary alcohols of the substituted acetylene series ; e.g., acetone gives 3-methyl-1-phenylbutyne-1-ol-3 :—

$$C_6H_5\,.\,C{\equiv}CH + CH_3COCH_3 \longrightarrow C_6H_5\,.\,C{\equiv}C\,.\,C(OH)(CH_3)_2$$

Moureu[3] noted an unusual reaction between phenylacetylene and paraformaldehyde, 1-phenylpropyne-1-ol-3 being formed :—

$$C_6H_5\,.\,C{\equiv}CH + CH_2O \longrightarrow C_6H_5\,.\,C{\equiv}C\,.\,CH_2OH$$

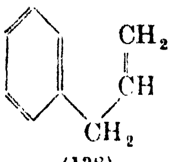
POLYNUCLEAR AROMATIC COMPOUNDS

Polynuclear aromatic compounds are divided into three main sections :—

(1) *Fused ring compounds*, in which at least two carbon atoms in one pair of rings are common, e.g., naphthalene.
(2) *Polyphenyl derivatives*, in which two or more aryl rings are directly joined by a single link, as in diphenyl.
(3) Substances containing two or more aryl rings separated by a carbon chain as in stilbene or triphenylmethane.

FUSED RING COMPOUNDS

Indene (139) is one of the simplest fused ring hydrocarbons, and forms a link between the simple aryl hydrocarbons of unsaturated side-chain and the members of this series, since the general properties of indene appear to be conditioned more by the *cyclo*pentene ring than by the benzene ring. A strong parallel exists between allylbenzene (138) and indene, and the properties of the latter are largely those of an unsaturated aliphatic body.



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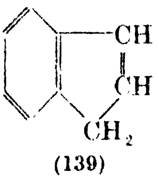
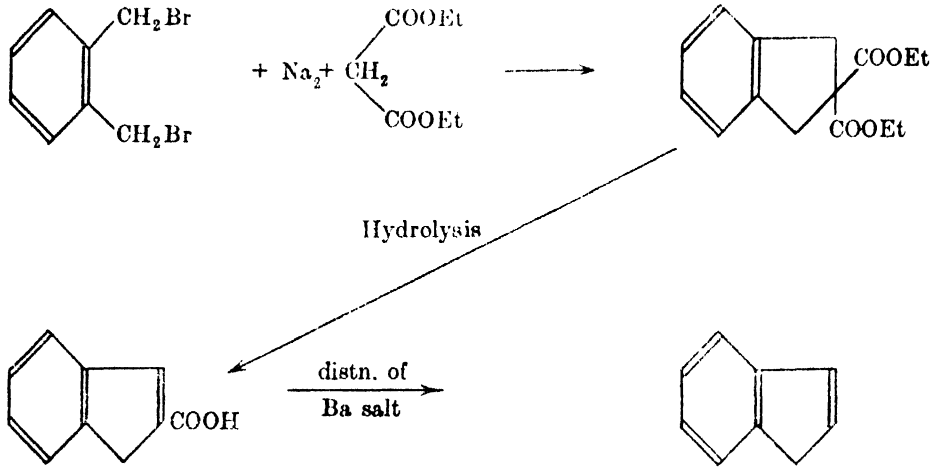


(139)

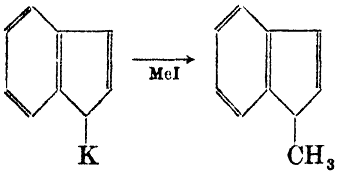
Indene was first isolated from coal-tar naphtha by Krämer and Spilker in 1890.[4] The fraction boiling between 176° and 182° is treated with picric acid solution when a crystalline picrate separates which after pressing and washing is decomposed by a brisk current of dry steam ; indene and water distil over. The fractionated indene melts at − 2° and boils at 182°, and possesses a strong disagreeable odour. Indene and its derivatives may be synthesised from dibromo-*o*-xylene and sodio-malonic ester :—

---

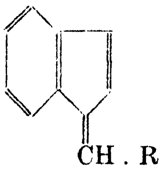
[1] *Organic Syntheses*, 1922, **2**, 67.
[2] Morgan, *J.C.S.*, 1876, **29**, 164.
[3] Moureu and Desmots, *C.R.*, 1901, **132**, 1224.
[4] Krämer and Spilker, *Ber.*, 1890, **23**, 3276.



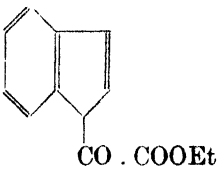
Chemically it behaves as though the extreme reactivity of *cyclo*pentadiene (the ring which is, of course, present in indene) has been tempered somewhat by the presence of the benzene ring. Thus, the reactivity of the methylene group persists ; indene forms a potassium or sodium derivative (140) which reacts readily with methyl iodide to give 1-methylindene (141).



(140) (141)

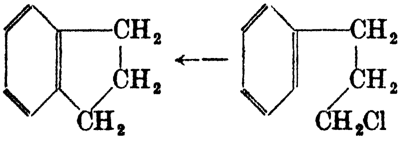


(142)

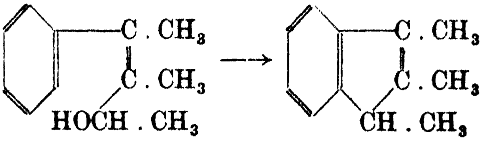


(143)

The hydrogen of the methylene group is also sufficiently active to take part in condensations with aldehydes in the presence of alcoholic potash[1] giving fulvene derivatives, e.g. (142) ; the active methylene group will also react with oxalic ester giving the compound (143). In addition, indene shows a strong tendency to polymerise and oxidises readily in air even at low temperatures. Catalytic reduction of indene leads to hydrindene (144) which can also be



(144) (145)



(146)

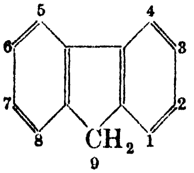
obtained in small yield by an internal Friedel-Crafts reaction using 3-phenyl-1-chloropropane (145) and anhydrous aluminium chloride.[2] Hydrindene is a colourless liquid, b. 177°, with but little reactivity of the type associated with indene itself.

---

[1] Thiele and Buhner, *Ann.*, 1906, **347**, 249 ; Thiele and Henle, *ibid.*, 296.
[2] Braun and Deutsch, *Ber.*, 1912, **45**, 1267.

Complex derivatives of indene are prepared by the methods elaborated by Koelsch [1] in which 3-phenylpropenol-1 derivatives are cyclised by dehydrating agents, e.g., 1, 2, 3-trimethylindene could be obtained by the method indicated in (146).

The hydrocarbon fluorene (147) is closely related to indene, and still preserves some of the reactivity of the *cyclo*pentadiene structure, although in a moderated form. Fluorene occurs in coal-tar, and is isolated therefrom in substantial quantity. Industrial fluorene, as prepared in the U.S.A., is a 90 per cent. concentrate, m. 109°, b. 295° ; pure fluorene has m. 116°, b. 295° ; it may be obtained by the pyrolysis of diphenylmethane (148) or by the decarboxylation of fluorene-9-carboxylic acid which loses carbon dioxide smoothly on boiling in aqueous solution.



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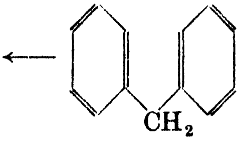

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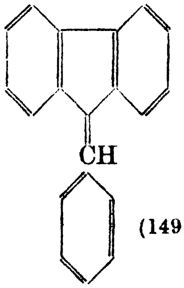

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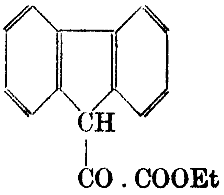
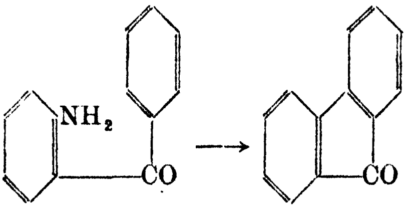


(150)

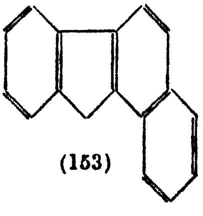
Fluorene forms potassium and sodium derivatives, and through them alkyl fluorenes, and the methylene group also evinces its unusual activity by condensations with aldehydes to give substances such as 9-benzalfluorene (149), and a condensation product with ethyl oxalate (150). Fluorene is oxidised readily to fluorenone (152).

The structure of fluorenone and its derivatives is confirmed by an extension of the Ullmann synthesis whereby diazotised *o*-amino-benzophenone (151) or its derivatives are warmed in solution with copper powder. Some *o*-hydroxybenzophenone is produced simultaneously.[2]



(151) (152)

The reactivity of the indene or *cyclo*pentadiene hydrogen persists even in such derivatives as chrysofluorene (153), but disappears, as might be expected, in fluoranthene (idryl) (154).



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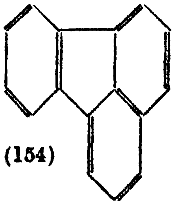

(154)

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[1] Koelsch, *J.A.C.S.*, 1932, **54**, 4744.

[2] Ullmann and Mallet, *Ber.*, 1898, **31**, 1694.

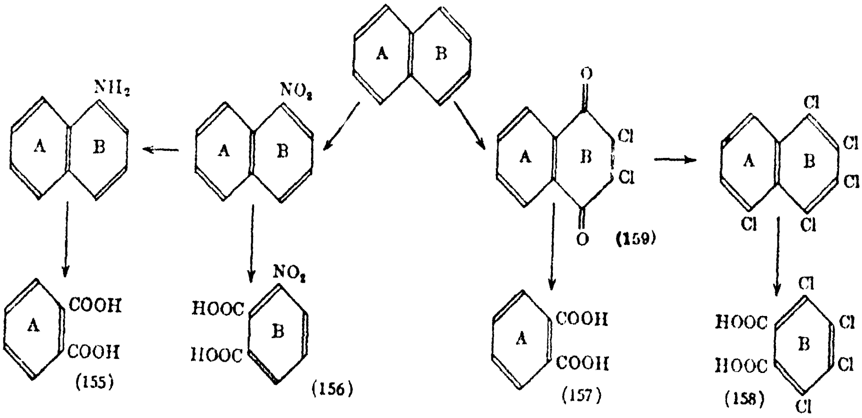
THE NAPHTHALENE SERIES

It has already been mentioned that naphthalene was the first pure hydrocarbon to be obtained from coal-tar. It exists therein in considerable quantity, passes over in the naphthalene oil and separates therefrom on cooling. The crude centrifuged (' whizzed ') naphthalene can be purified by a series of pressings, extractions and distillation until it sublimes as pure white plates, having a very characteristic odour. Naphthalene melts at 81° and boils at 218°. It sublimes extremely readily, and advantage is taken of this property for purposes of purification.

THE STRUCTURE OF NAPHTHALENE

In 1866 Erlenmeyer, senr., suggested for the formula of naphthalene what he termed " two ortho-condensed benzene rings ", thus, at one and the same time correctly indicating the structure of the hydrocarbon and extending the use of the term ' condensed ' to apply to ring structure with more than one carbon atom in common. In 1869 Gräbe confirmed Erlenmeyer's formula by a series of conversions of various naphthalene derivatives to phthalic acids,

TABLE XXVIII



thus succeeding in ' labelling ' each portion of the naphthalene structure. These substances are shown in Table XXVIII. Naphthalene gives a nitronaphthalene on nitration, which on destructive oxidation yields 3-nitrophthalic acid (156); if, however, the nitro-body is reduced prior to oxidation, to naphthylamine, unsubstituted phthalic acid is obtained (155). Consequently, since when either ' A ' or ' B ' portion of naphthalene is destroyed a benzene ring still remains, it follows that naphthalene must possess the ' *ortho*-condensed ' benzene structure, put forward by Erlenmeyer. Gräbe devised a similar set of experiments with dichloronaphthoquinone; when this substance (159) is oxidised, it yields phthalic acid (157); if, however, it be converted to pentachloro naphthalene by phosphorus pentachloride, prior to oxidation, tetrachlorophthalic acid (158) is obtained.

Confirmation of this structure is given, in some measure, by the synthesis of naphthalene achieved by Fittig.[1] 1-Phenylbutene acid-4 (phenyl*iso*crotonic acid) (160) a homologue of cinnamic acid, loses the elements of water on heating to give α-naphthol (161) and this on distillation with zinc dust yields naphthalene, this simple change being strong presumptive evidence for the structure (162).

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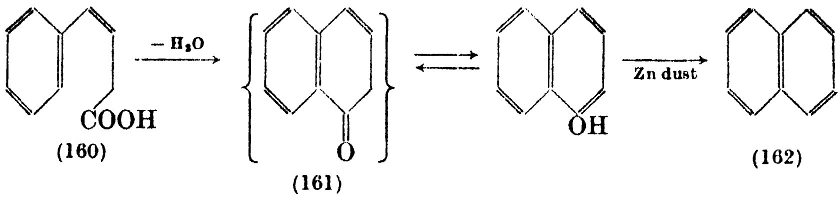
[1] Fittig and Erdmann, *Ber.*, 1883, **16**, 43.

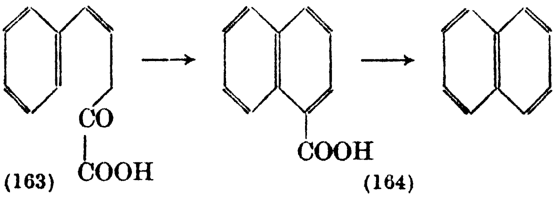


(160) (161) (162)

In general, syntheses of naphthalene are of two types, those which, like the one described above, involve the ring closure of a mono-substituted benzene derivative, carrying at least four carbon atoms in its side-chain, and those in which an *o*-disubstituted benzene derivative is condensed with an aliphatic compound.

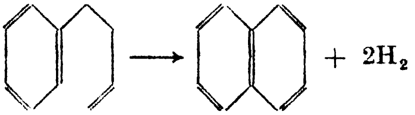
Further examples of the first type are :—

(1) The ring closure of cinnamyl pyruvic acid (163) in the presence of concentrated hydrochloric acid at 110–120° to naphthoic acid (164), from which naphthalene may readily be obtained by distillation with lime.[1]



(163) (164)

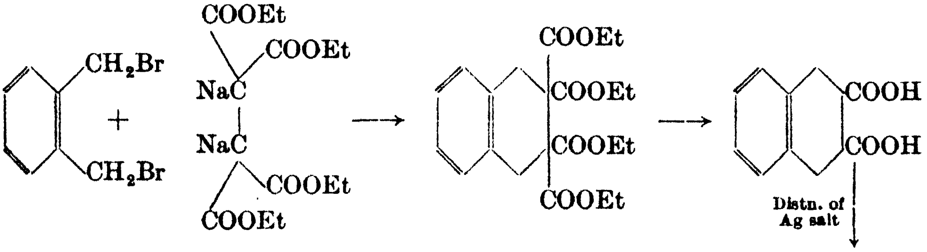
(2) The pyrolysis of 1-phenylbutene-3 (165).



(165)

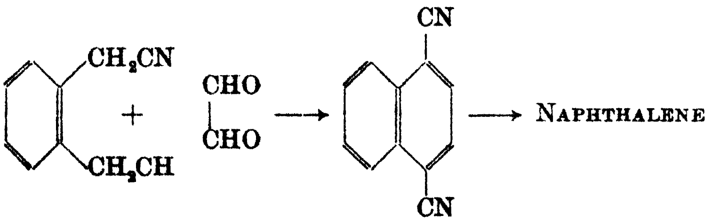
Examples of the second type are :—

(1) The methods of Baeyer and Perkin in which *o*-xylylene dibromide and disodium ethane tetracarboxylic ester are condensed through the stages indicated in the formulæ below :—



NAPHTHALENE

(2) Hinsberg's method[2] in which *o*-xylylene cyanide is condensed with glyoxal or an α-diketone :—



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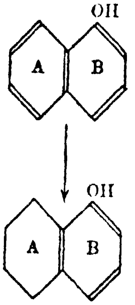
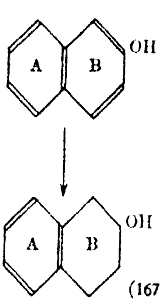
[1] Erlenmeyer and Kunlin, *Ber.*, 1902, **35**, 384.

[2] Hinsberg, *ibid.*, 1910, **43**, 1360.

Bamberger[1] carried out much research on the structure of naphthalene. Briefly, his thesis was that whilst accepting the carbon skeleton of Erlenmeyer's structure, he denied the symmetry and true aromatic character of the nuclei, seeking to place naphthalene in a class by itself distinct from benzene and truly aromatic hydrocarbons. Much of Bamberger's arguments are based on the behaviour of naphthalene towards reducing agents ; thus, he observed that although tetrahydronaphthalene (tetralin) was readily obtained by reduction of naphthalene in amyl alcohol with sodium, the reduction stopped at this point, and sterner measures were required to effect reduction of the six remaining carbon atoms. Further, when α- and β-naphthol are reduced the former gives a tetrahydro body in which reduction has taken place in the so-called alicyclic ring (166), the hydroxyl remaining in the aromatic ring B, whilst when β-naphthol is reduced the hydroxyl remains in the reduced or alicyclic ring (167).

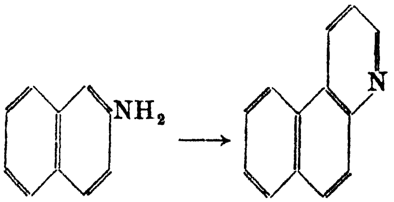


(166)

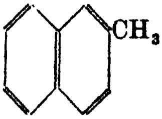


(167)

Numerous chemical differences can be adduced to demonstrate that *ar*-α-tetrahydronaphthol (*ar*-α-tetralol) possesses a truly phenolic hydroxyl whilst that of *ac*-β-tetralol is entirely aliphatic. From this Bamberger concluded that the true benzenoid structure is only produced when reduction of the second ring takes place, or conversely that there is no truly aromatic ring in naphthalene itself. That this, on his part, was largely juggling with words can be seen if one pauses to ask what exactly is meant by 'truly aromatic'. One factor in the chemistry of naphthalene that is intimately concerned with its structure is that pronounced tendency of naphthalene and its derivatives to react in the 'α-' position, in preference to the 'β' ; indeed, when β-substituted compounds are formed it is usually the result of a rearrangement of a previously formed α-derivative. As instances of this, one may cite the tendency of β-naphthylamine (168) to form an angular, in preference to a linear, phenanthridine (169)



(168) (169)



(170)

by Skraup's reaction ; and the fact that there is no simple method of synthesising β-methylnaphthalene (170). Marckwald[2] carried out much work on this subject and endeavoured to account for the behaviour of naphthalene as a result of the fixation of the Kekule formula with the double bond between the α- and β-positions. This subject is more fully dealt with in Vol. III, Chapter VI.

Naphthalene forms a large number of substitution products, mono substitution products are usually designated as either ' α ' or ' β ', as, for example, in the nitro-naphthalenes (171 and 172) :—

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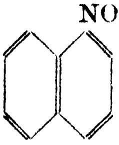
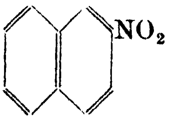
[1] A summary of Bamberger's work on the naphthalene problem is given in *Ann.*, 1890, **257**, 1.

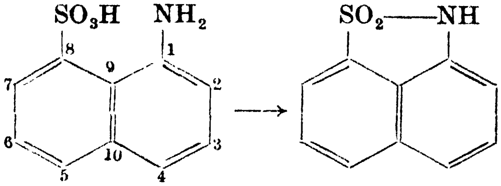
[2] Marckwald, *Ann.*, 1893, **274**, 331 ; 1894, **279**, 1.



α (171)



β (172)



(173) (174)

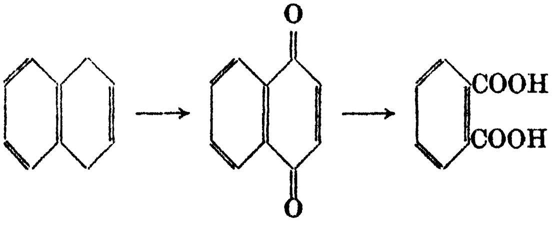
There are ten disubstituted naphthalenes when the substituents are identical, and fourteen when different. The presence of substituents in the 1 : 8-positions is sometimes signified by the use of the prefix ' peri ', as in ' peri naphthylamine sulphonic acid ' (173). The substituents of peri compounds appear to be more easily able to interact than those in other adjacent positions ; thus, the naphthylamine sulphonic acid (173) just referred to, passes into a sultam (174) with great ease.

The various possibilities in the higher substituted naphthalenes are shown in Table XXIX :—

TABLE XXIX

No. of substituents	Variety of substituents	No. of isomers
1		2
2	The same	10
	Different	14
3	All the same	14
	Two the same	42
	All different	84
4	All the same	22
	Two the same	210
	Two pairs identical	114
	Three the same	70
	All different	420
5	All different	1680
8	All different	10080

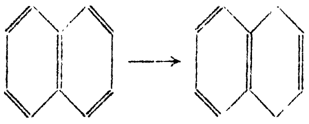
The oxidation of naphthalene proceeds readily, and can be stopped at the stage of naphthoquinone (175), or of phthalic acid (176), quite easily.

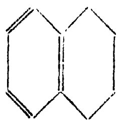


(175) (176)

It is doubtful whether or not these two substances should be regarded as sequential ; the quinone is obtained by acetic/chromic acid oxidation, and the phthalic acid by oxidation with sulphur trioxide in the presence of mercury.

Reduction of naphthalene is comparatively easy :—


(177)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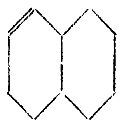
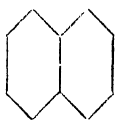
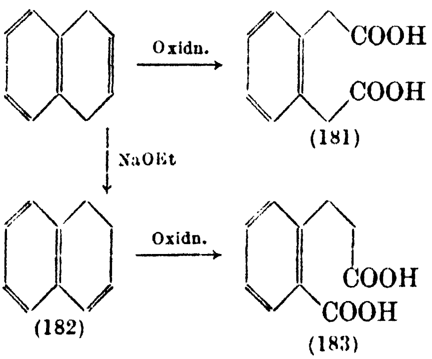

(179)


(180)

Heated in alcoholic solution with sodium, naphthalene yields 1, 4-dihydronaphthalene (177) ; with hydrogen and a nickel salt the process stops at tetrahydronaphthalene. Thus far, there is no doubt as to the structure of the two compounds formed, and the behaviour of both is that of an aromatic hydrocarbon with an unsaturated side-chain. Thus, 1-4 dihydronaphthalene yields *o*-phenylene diacetic acid (181) on mild oxidation. On heating with sodium ethylate for some time, it passes into the 1-2-dihydro compound (182)[1] which on oxidation gives *o*-carboxyhydrocinnamic acid (183).



The hexahydro- and octahydro-derivatives of naphthalene are only obtainable by indirect routes, and as these involve a knowledge of the decahydro-derivative, this substance will be considered first. When naphthalene is subjected to vigorous hydrogenation in the presence of a platinum catalyst, decahydronaphthalene is obtained. This substance, like cyclohexane, has the potentiality of existing in *cis*- and *trans*-form, which are indicated in Fig. II. This is very beautifully demonstrated by the isolation of the four racemic tetradecahydro-β-naphthols (decalols) also shown in Fig. II, and is referred to more fully in Vol. III.

Decahydronaphthalene, more often referred to as ' decalin ', is systematically bicyclo[4, 4, 0]decane ; the *cis*- and *trans*-forms, b. 193° and 185° respectively, are separable by systematic fractionation. To obtain the *cis*-form naphthalene is reduced by hydrogen in the presence of platinum and the product, which contains over 80 per cent. of the *cis*-form, is distilled through an all-glass still and column with a reflux ratio head set for a high ratio. If a nickel catalyst be used, the *trans*-form predominates, and may be isolated in a similar way.

The di-, hexa- and octahydro-derivatives of naphthalene are difficult to prepare and correspondingly less well-known. Chlorination of decalin gives mono- and di-chloro derivatives, the former predominating. The fraction b_{15} 110-112° is *cis*-chlorodecalin (184), and on boiling with aniline for two hours gives the *cis*-octalin (185). The dichloro-derivative is of unknown orientation,

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[1] Straus and Lemmel, *Ber.*, 1913, **46**, 232.

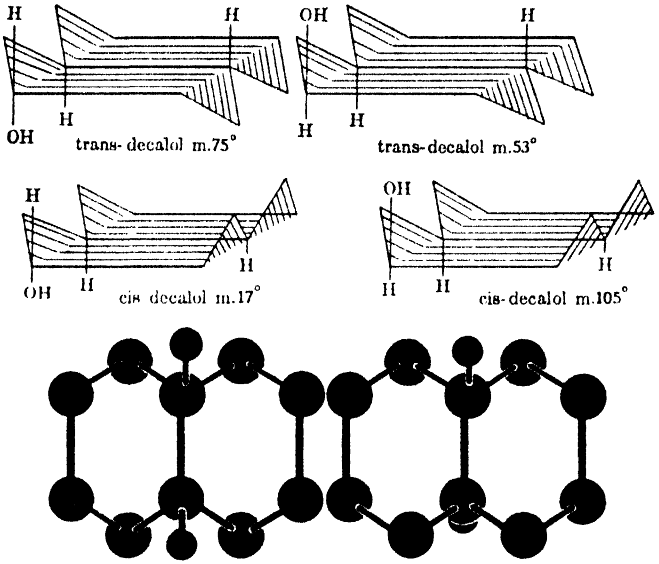
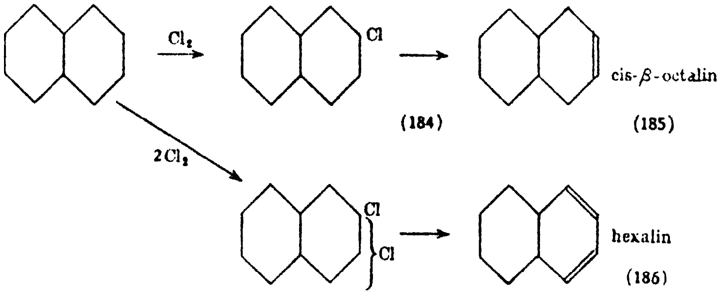
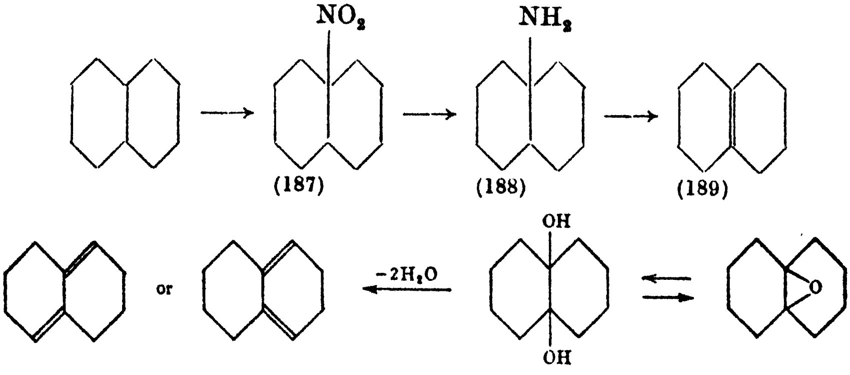


FIG. II

but yields a hexalin (186) on heating with aniline or quinoline. Another octalin has been investigated by Nametkin and his assistants.[1] When decalin is nitrated, the angular tertiary nitro compound is formed (187); this may be reduced to the amino compound (188) which, on boiling in hydrochloric acid





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[1] Nametkin and Madaer-Ssichev, *Ber.*, 1926, **59B**, 370.
Nametkin and Gagloleva, *J. Russ. Phys.-Chem.*, 1929, **61**, 535.

with potassium nitrite, yields an octalin, the structure of which (189) is ascertained by its yielding sequentially an octalin oxide and glycol which are intraconvertible, indicating a di-tertiary structure, since secondary/tertiary glycols yield ketones on dehydration.

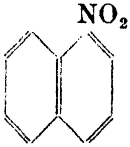
Some of the properties of hydrogenated naphthalenes are summarised in Table XXX.

TABLE XXX

	m.p.	b.p.	S.G.
Naphthalene	81°	218°	$[d]_0^{18}$ 1·1508
1, 4-Dihydronaphthalene	25°	212°	
1, 2, 3, 4-Tetrahydronaphthalene	—30°	207°	
1, 2, 3, 4, 9, 10-Hexahydronaphthalene	(n_D^{20} 1·5322)	75–76°/8 mm.	$[d]_4^{20}$ 0·9726
1, 2, 3, 4, 5, 6, 7, 8-Octahydronaphthalene	—	88–89°/14 mm.	$[d]_4^{20}$ 0·92
1, 2, 3, 4, 6, 7, 9, 10-Octahydronaphthalene	(n_D 1·4959)	72–73°/15 mm.	$[d]_4^{22}$ 0·915
Decahydronaphthalene *cis*	(n_D^{20} 1·48279)	193°	$[d]^{20}$ 0·898
Decahydronaphthalene *trans*	(n_D^{20} 1·47009)	185°	$[d]_4^{20}$ 0·872

Naphthalene and all its hydrogenated derivatives can be nitrated, the nitration of decalin requiring very severe conditions.[1]

The nitration of naphthalene is readily accomplished by a nitrating acid of somewhat less concentrated composition than that used for benzene. The α-nitro-compound is obtained almost exclusively (190) in mononitration,[2] and a mixture of the 1, 5- and 1, 8-dinitro compounds (192), on the use of stronger acids. The chlorination of naphthalene is a more complicated subject; in sunlight naphthalene in the solid state readily absorbs chlorine yielding a tetrachloro-addition derivative. On the other hand, direct chlorination under suitable conditions gives the mono chloro derivatives (95 per cent. α-chloronaphthalene, and 5 per cent. β-chloronaphthalene) which can be separated by the method of Britton and Reed[3]; further chlorination leads to higher substitution products, and finally to a wax-like solid, of valuable dielectric properties.[4] Naphthalene sulphonates readily, the α-sulphonic acid being first formed; this, on heating above 180° in sulphuric acid solution, passes over into the β-acid. In nearly all the di-, tri- and tetrasulphonic acids (of which eighteen are known) most have at least one sulphonic group in the α-position. This tendency to reaction through the α-hydrogen is characteristic of naphthalene, and is carried even to such lengths as the preferential elimination of α-hydrogen in the treatment of naphthalene with anhydrous aluminium chloride when perylene (193) is obtained.



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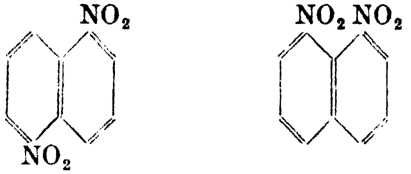

(192)

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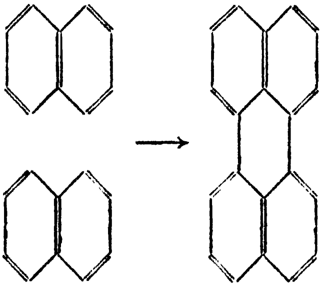
[1] Nametkin, *loc. cit.*, p. 165.

[2] Witt, *J.S.C.I.*, 1887, **10**, 216.

[3] Britton and Reed, *U.S.P.*, *1,917,822*.

[4] Sold under the trade name ' Halowax '.



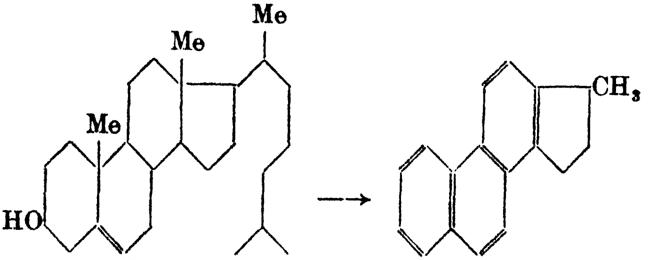
(193)

ALKYL AND RELATED NAPHTHALENE DERIVATIVES

α- and β-Methylnaphthalenes occur in coal-tar from which they are separated in considerable quantity. The α-compound m. − 22°, b. 243°, has few applications except in the standardisation of Diesel fuels. It is the component of low cetene (antiknock) value ; but the β-compound m. + 35°, b. 245° is used to a limited extent in the pure state for the synthesis of vitamin K analogues. The two are separated by freezing out the crude β- which then has a setting point of 31°, and may be purified by partial freezing or crystallisation. Whilst α-methylnaphthalene is readily synthesised, as, for example, by the Würtz-Fittig reaction between α-bromonaphthalene, methyl iodide and sodium :—

$$C_{10}H_7Br + I\,.\,CH_3 + Na_2 \longrightarrow C_{10}H_7\,.\,CH_3 + NaI + NaBr$$

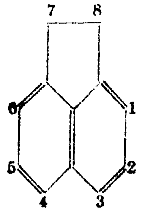
the β-methyl derivative has never been synthesised by any convenient route, the Würtz-Fittig reaction entirely breaking down with β-bromonaphthalene, and the Friedel-Crafts reaction being equally unsatisfactory. Numerous di- and tri-methyl derivatives, together with ethyl and isopropyl substituted homologues of naphthalene have been prepared in connexion with researches on the terpene family, e.g., sapotalene (1, 2, 6-trimethylnaphthalene) and cadalene (1, 6-dimethyl-4-isopropylnaphthalene). They are discussed more fully in Chapter IX. Much of our knowledge of the higher alkyl substituted naphthalene derivatives is due to the growth of the technique of structural elucidation by means of sulphur or selenium dehydrogenation. Thus, complex ring structures in which the carbon structure is partially or fully hydrogenated are not easily identified by conversion to recognisable derivatives. If, however, they are heated with selenium (or in simple cases, sulphur), hydrogen or alkyl selenide or sulphide is evolved, and the hydrocarbon is converted to the corresponding aromatic derivative, usually merely by loss of hydrogen and without serious structural change. The aromatic hydrocarbon can often be identified without much difficulty, and can often be synthesised, thus elucidating the skeleton of the original substance. One example is the dehydrogenation of cholesterol (194) to a methyl derivative of *cyclo*pentenophenanthrene (195).



(194) (195)

Much of our knowledge of this reaction is due to the work of Ruzicka, Diels and others who have used it with conspicuous success in disentangling the difficult constitutional problems of the sterols and related products.[1]

Among the alkyl derivatives of naphthalene may be included the acenaphthene family. Acenaphthene itself (196), a 1, 8-ethylene derivative of naphthalene, was first isolated by Berthelot from coal-tar. It is isolated from the forerun of the anthracene oil, and is available commercially as a 95 per cent. product, freezing at 91° and boiling at 277°. The pure substance forms long white needles, m. 95°, b. 278°, with a faint but not unpleasant odour. It oxidises extremely easily to acenaphthene quinone (198) and to naphthalic acid (199), a tendency which is characteristic of *peri*-bridges of this type. The reactivity of the bridge makes it somewhat difficult to obtain ordinary substitution products of acenaphthene. It is, however, possible to nitrate acenaphthene in the ' 3 ' position directly, and in the ' 1 ' position by the use of benzoyl nitrate.[2] Chlorination, bromination and sulphonation almost always lead to a ' 3 ' derivative, and the concentration of reactivity in the ' 3 ' and ' 4 ' positions of acenaphthene is shown in a remarkable manner by its condensation with succinic anhydride to form a *peri*succinoylacenaphthene [3] (200) which may be reduced to a *peri*-tetramethylene derivative (201) by sodium ethylate and hydrazine (Wolff-Kishner).



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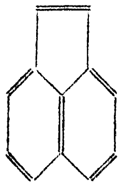

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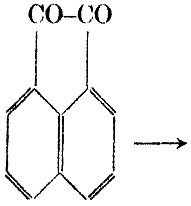

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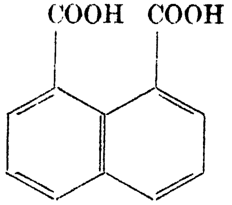

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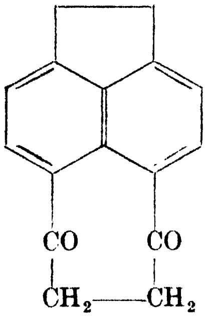
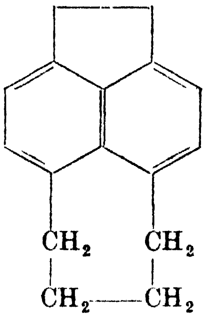
(200)





(201)

The oxidation of acenaphthene to acenaphthylene (197) m. 92°, by loss of hydrogen from the *peri*link may be attained by heating acenaphthene alone or by passing its vapour over heated litharge.

ANTHRACENE

Dumas and Laurent [4] first isolated anthracene in 1832, and it is one of the more prominent constituents of the higher boiling fractions of coal-tar. When the so-called ' anthracene oil ' from tar (boiling 270–400°) is allowed to stand for some days, crude anthracene (containing carbazole and phenanthrene) separates and by centrifuging and hot pressing the solid material, a press-cake containing 40–50 per cent. of anthracene is obtained. If this cake is milled and digested with hot crude pyridine bases, it is almost entirely soluble, but on cooling most of the anthracene crystallises out, leaving the carbazole and phenanthrene behind in solution. Two successive treatments of this character followed by centrifuging and pressing give the industrial 90 per cent. anthracene. Further purification by a variety of procedures, including distillation in superheated steam, gives an industrial '98 per cent. anthracene' manufactured chiefly in America. It is almost white, melts at 213°, and boils at 341°. The pure substance is colourless, but shows a blue fluorescence, m. 218°, b. 342°.

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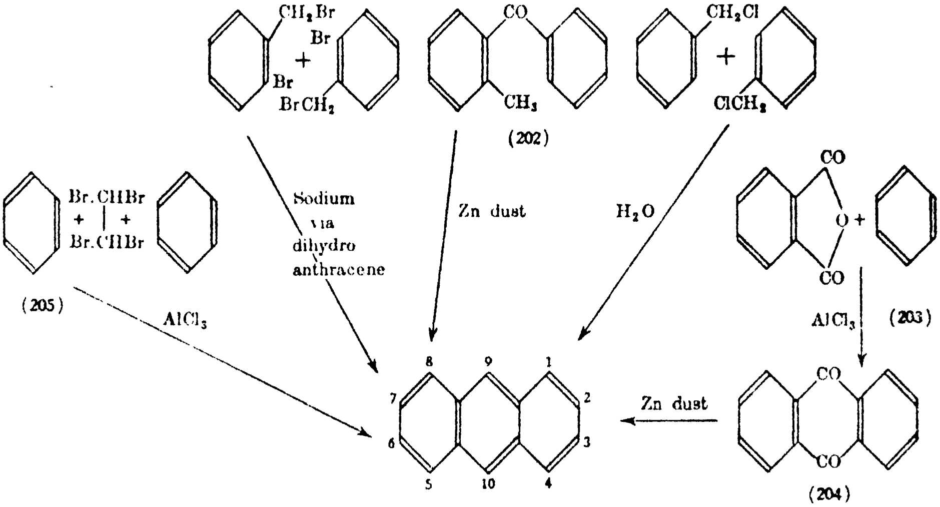
[1] Diels, Gädke and Körding, *Ann.*, 127, **459**, 1 ; Diels and Rickert, *Ber.*, 1935, **68**, 267 ; Ruzicka and Meyer, *H. Chim. Acta*, 1921, **4**, 508.

[2] Morgan and Sheasby, *J.S.C.I.*, 1925, **44**, 408T.

[3] Fieser and Peters, *J.A.C.S.*, 1932, **54**, 4347.

[4] Dumas and Laurent, *Ann.*, 1833, **5**, 10.

Synthesis of anthracene can be carried out by a wide variety of procedures; the earliest, that of Behr and Dorp in 1873,[1] consists in heating 2-methyldiphenylketone with zinc dust (202). An alternative method discovered about the same time by Limpricht, consists in heating benzyl chloride with water under pressure.[2] The reaction [3] which has given rise to the most widely used process for the manufacture of anthracene derivatives is the condensation of phthalic anhydride and benzene (203) in the presence of anhydrous aluminium chloride to give anthraquinone (204) which can be reduced to anthracene by distillation with zinc dust. None of these reactions points with certainty to the double ortho linkage of the two benzene rings, so that the elimination of four molecules of sodium bromide from two of *o*-bromobenzyl bromide (205) in the presence of sodium,[4] giving dihydroanthracene, oxidisable on the least provocation to anthracene itself, is regarded as evidence of the validity of the usual formula insofar as the carbon skeleton is concerned.



The reaction of Anschütz,[5] whereby one molecule of tetrabromoethane is induced by anhydrous aluminium chloride to react with two molecules of benzene (205) to give anthracene, has been adduced as evidence that the '9' and '10' carbon atoms of anthracene are united by a bond; the problem of anthracene structure is not so simple as might appear from this reaction. Since the synthesis of Anschütz there has been a gradually increasing mass of evidence against the *para*-bond structure. This evidence, which is discussed in detail in Vol. III, culminated in the X-ray analysis of Meyer in 1928, which showed that all the carbon atoms of anthracene lie in the same plane, which implies that the '9' and '10' carbon atoms are equally as distant from one another as they would be in a normal benzene ring; valency links between carbons so far apart have never yet been encountered, and are extremely improbable. The most satisfactory static formulæ for anthracene are the *o*-quinonoid structures (206) and (207) similar to those advanced by Armstrong in 1890, either of which is capable of demonstrating the power which anthracene undoubtedly possesses of restoring the benzenoid nature of its two outer rings by the saturation of the '9' and '10' carbon atoms (208). This activity of the meso carbon atoms is particularly marked, even sunlight being capable of converting anthracene to a non-reactive dimer, probably having the structure (209). This argument is also strengthened by the marked tendency of anthracene to oxidise readily in the meso positions to anthraquinone.

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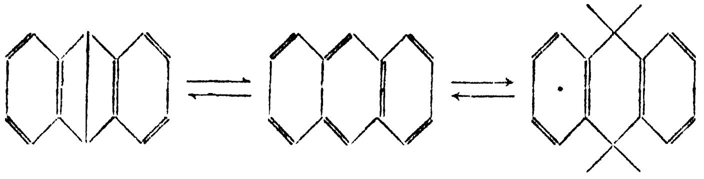
[1] Behr and Dorp, *Ber.*, 1873, **6**, 754.

[2] Limpricht, *ibid.*, 1874, **7**, 276.

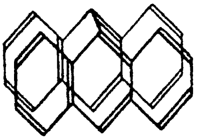
[3] Behr and Dorp, *ibid.*, 1874, **7**, 578.

[4] Jackson, White, *ibid.*, 1879, **12**, 1965.

[5] Anschütz, *ibid.*, 1883, **16**, 623.



(206) (207) (208)



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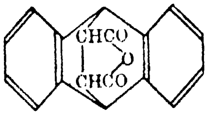
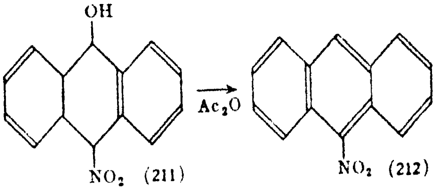


(210)



(211) (212)

The chemical properties of anthracene appear to be conditioned largely by its meso-carbon atoms. Thus, chlorination, reduction and oxidation are all concerned with these atoms, a dichloro compound being formed by addition, reduction giving 9, 10-dihydroanthracene and oxidation, anthraquinone. In addition, it may be added that the behaviour of anthracene as a diene capable of adding to maleic anhydride to give the compound (210) not only confirms the structure for anthracene, but gives an additional example of its readiness to react through the 9, 10 positions. The nitration of anthracene is anomalous. The tendency is to produce anthraquinone by oxidation through the HNO_3 addition product (211), but in acetic anhydride the 9-nitro compound is formed (212).

PHENANTHRENE

In 1872 Graebe,[1] working with a quantity of crude anthracene residues, and, independently, Fittig and Ostermeyer,[2] working with anthracene oil, discovered the hydrocarbon phenanthrene, which they showed was isomeric with anthracene. Graebe and Liebermann,[3] in their researches on anthracene, had been inclined to ascribe the angular formula (213) to that hydrocarbon which would have left the linear structure for phenanthrene itself. Fittig and Ostermeyer, however,

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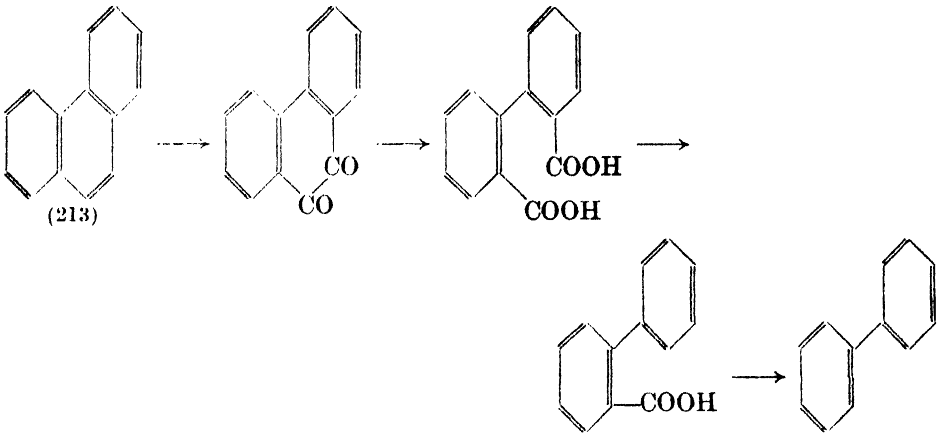
[1] Graebe, *Ber.*, 1872, **5**, 861, 986. [2] Fittig and Ostermeyer, *ibid.*, 1872, **5**, 933.
[3] Graebe and Liebermann, *Ann.* (Supplement), 1870, **7**, 315.


(213)

degraded phenanthrene to diphenyl by the reactions indicated in the formulæ above, thus proving that this hydrocarbon is correctly represented by the angular formula.

The removal of phenanthrene from anthracene and carbazole with which it occurs in coal-tar is by no means a simple operation. If the anthracene fraction be diluted with coal-tar naphtha and heated with caustic potash the carbazole present is almost completely converted into the potassium derivative, which is insoluble. The liquid portion, after removal of the potassium carbazole, is cooled, anthracene crystallising out. Fractionation of the mother liquor from this operation will give a product containing 50–60 per cent. of phenanthrene, and by recrystallisation, an industrial phenanthrene is obtained which contains 90 per cent. of the hydrocarbon, has a setting point of 102°, and boils at 337°. Further purification by physical means is almost impossible as phenanthrene and anthracene form mixed crystals of a m.p. higher than that of phenanthrene alone.[1] To obtain pure phenanthrene, the crude anthracene in admixture is oxidised to anthraquinone, either by nitric acid in alcohol,[2] or by such concentrations of chromic acid in acetic acid,[3] as will leave the phenanthrene unattacked. After dissolving out the anthraquinone with alcohol the residue is heated in nitrobenzene solution with a little maleic anhydride[4] to remove any residual traces of anthracene, filtered from the Diels-Alder addition compound and allowed to cool; in this way fairly pure phenanthrene crystallises. During the whole of these operations traces of a sulphur compound (? diphenylene sulphide) follow the phenanthrene, and must be removed by refluxing over sodium if the phenanthrene is to be used for catalytic hydrogenations, since its presence inhibits the catalysts. Phenanthrene forms large triclinic plates, m. 99–100°, b. 340°.

Few synthetic methods of approaching phenanthrene derivatives have proved successful except for the purpose of establishing structure, as the yields are poor, save in exceptional instances. One of the most interesting examples of these syntheses is that devised by Pschorr,[5] as an extension of the diazo elimination reaction for diphenyl derivatives. Thus, *o*-nitrobenzaldehyde undergoes a Perkin condensation with phenylacetic acid (214) to give phenyl-*o*-nitrocinnamic acid (215); this can be reduced to the corresponding amine

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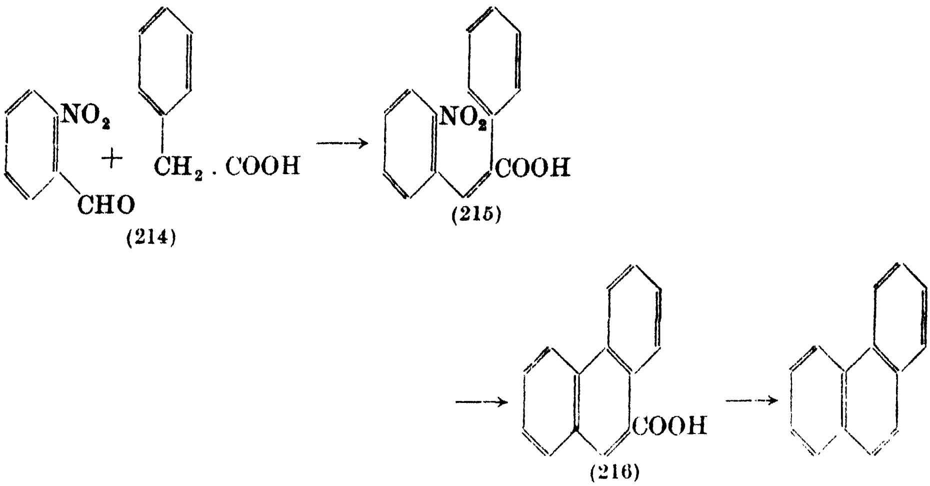
[1] Clark, *J. Ind. Chem.*, 1919, **11**, 204.

[2] Sandquist. As quoted from his dissertation (Uppsala, 1912); Cohen and Cormier, *J.A.C., S.*, 1930, **52**, 4363.

[3] Mortimer and Murphy, *J. Ind. Eng. Chem.*, 1923, **15**, 1140.

[4] Clar, *Ber.*, 1932, **65**, 852.

[5] Pschorr, *ibid.*, 1896, **29**, 496.

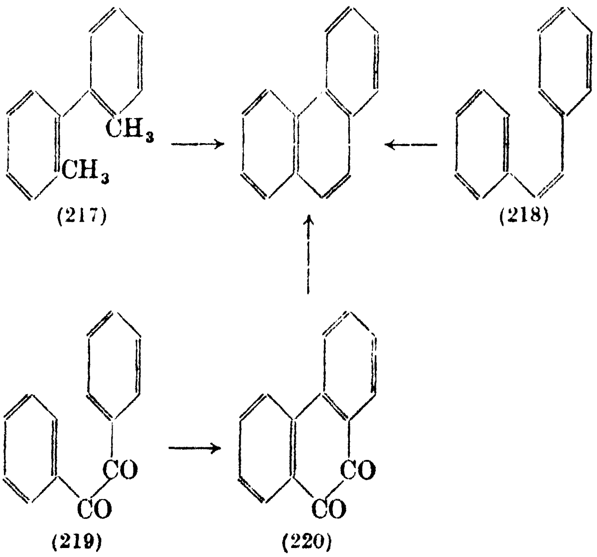


(214) (215) (216)

which, on diazotisation and warming with copper powder, annulates to phenanthrene-9-carboxylic acid (216), which may, if desired, be decarboxylated to phenanthrene itself.

Other methods of synthesis of phenanthrene include :—

(1) The pyrolysis of *o*-ditolyl or stilbene (217) and (218) :—



(217) (218) (219) (220)

(2) The action of anhydrous aluminium chloride on benzil[1] (219) whereby phenanthrene-quinone (220) is obtained and may be reduced to phenanthrene itself.

(3) The Bardhan and Sengupta[2] synthesis of phenanthrene derivatives involves the condensation of ω-bromoethylbenzene with *cyclo*hexanone-2-carboxylic ester in the presence of potassium :—

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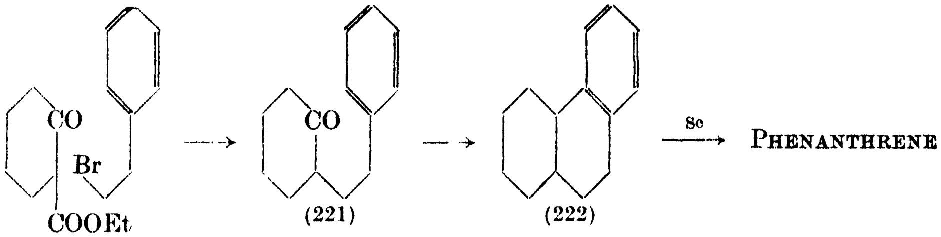
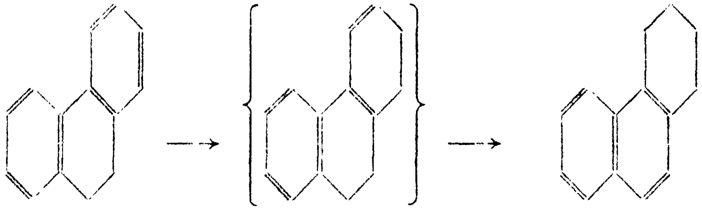
[1] Scholl and Schwarzer, *Ber.*, 1922, **55**, 324.

[2] Bardhan and Sengupta, *J.C.S.*, **1932**, 2520 and 2798.



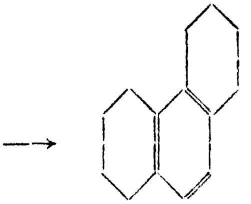
to give the ketone (221); this may readily be reduced by sodium in moist ether to the corresponding alcohol (not shown in the formulæ), and this ring closed to octahydrophenanthrene (222) with phosphorus pentoxide. Dehydrogenation with selenium gives the parent hydrocarbon phenanthrene itself.

Phenanthrene is more reactive than naphthalene, but less so than anthracene. The reduction of phenanthrene has been carefully studied by Schroeter, and much of the earlier (and inaccurate) information on this subject has been clarified.[1] Catalytic hydrogenation attacks the bridge-link first, giving the 9, 10-dihydrophenanthrene (223), followed by the 1, 2, 3, 4-tetrahydro derivative (224).

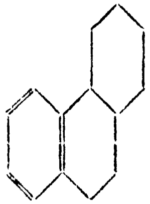


9, 10-Dihydro-
m. 34–35°
(223)

1, 2, 3, 4-Tetrahydro-
m. 33–34°
(224)



1, 2, 3, 4, 5, 6, 7, 8-
Octahydro-
m. 16·7°
(225)



1, 2, 3, 4, 9, 10, 11, 12-
Octahydro-
phenanthrene
(226)

formed obviously by a rearrangement from the intermediate labile form. The 9, 10-dihydro-derivative can be prepared very easily in over 90 per cent. yield by using a copper-chromium catalyst supported on barium oxide.[2] Further catalytic reduction gives the symmetrical octahydro-derivative[3] (225). An isomer of this hydrocarbon, the 1, 2, 3, 4, 9, 10, 11, 12-octahydro-compound (226) may be obtained by the Bardhan-Sengupta synthesis (*q.v.*) or by Rabe's method,[4] in which a dihydronaphthoic ester (227) is condensed by Michael's reaction with acetoacetic ester, thus giving diketoöctahydrophenanthrene carboxylic ester (228), which is decarboxylated on hydrolysis to diketoöctahydrophenanthrene, which latter is reduced by Clemmensen's method to octahydro-

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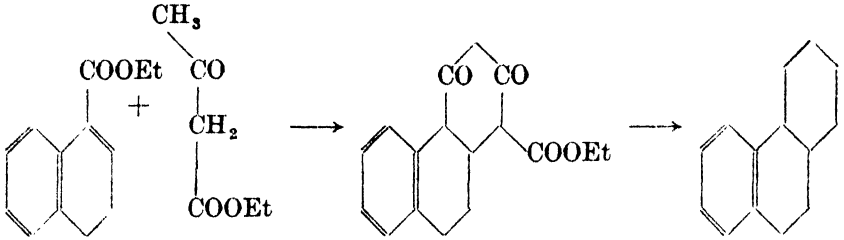
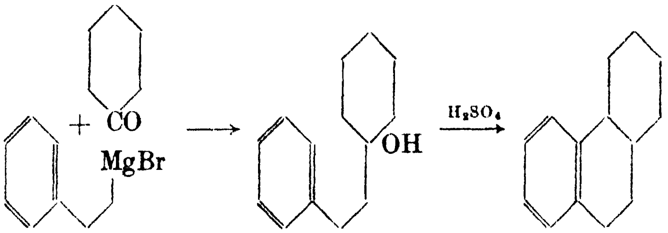
[1] Schroeter, *Ber.*, 1924, **57**, 2025; with Muller and Huang, *ibid.*, 1929, **62**, 645.
[2] Burger and Mosettig, *J.A.C.S.*, 1935, **57**, 2731.
[3] v. de Kamp and Mosettig, *ibid.*, 1935, **57**, 1107.
[4] Rabe, *Ber.*, 1898, **31**, 1896.



(227) (228) (229)

phenanthrene (229) itself. An even simpler method is that of the condensation of *β*-phenylethyl magnesium bromide with *cyclo*hexanone (230)[1]; the tertiary

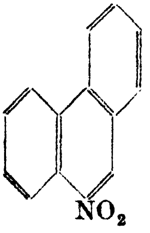


(230) (231)

alcohol (231) so formed is dehydrated and annulates simultaneously when treated with sulphuric acid.

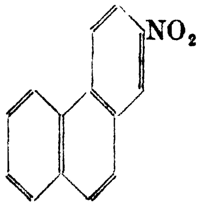
Phenanthrene is readily oxidised to phenanthrenequinone, and by further oxidation diphenic acid is produced, this method serving as a convenient means for the elucidation of the structure of phenanthrene derivatives substituted in positions other than 9 or 10.

Nitration of phenanthrene proceeds mainly to the 9-nitrobody (232), but quite appreciable amounts of the 2- and 4-nitro compounds are formed (233) and (234). Sulphonation gives a mixture of isomers, the separation of which



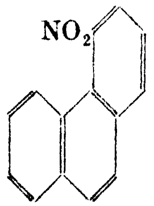
9-nitro

(232)



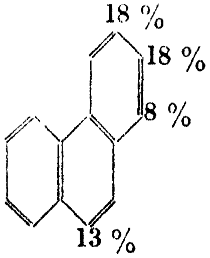
2-nitro

(233)



4-nitro

(234)



(235)

was elucidated by Werner and his co-workers with results which are indicated in (235). Claims made by Willgerodt and Albert[2] that the Friedel-Crafts reaction includes entry of acyl groups in the 9-position appear to be incorrect; with acetyl chloride it has been shown[3] that the bulk of the acetyl compound formed (64 per cent.) is the '3'-derivative, together with some 15 per cent. of the 2-derivative.

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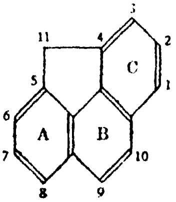
[1] Perlman, Davidson and Bogert, *J. Org. Chem.*, 1936, **1**, 288.
[2] Willgerodt and Albert, *J. Pr. Chem.*, 1911, **84**, 383.
[3] Mosettig and v. de Kamp, *J.A.C.S.*, 1930, **52**, 3704.

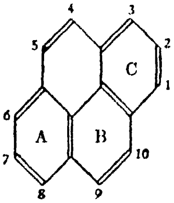
The compounds of phenanthrene have assumed a very high importance by virtue of their widespread occurrence as part of many important biological substances. Those requiring further details are referred to Fieser's Monograph (see Appendix I), and also to Chapter X.

OTHER CONDENSED BENZENE NUCLEI

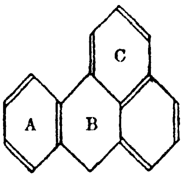
The formulæ below indicate a number of hydrocarbons which constitute examples of the various families of condensed aromatic nuclei :—



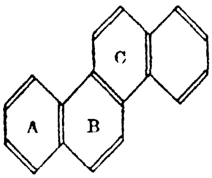
Phenanthrenyl methane (236)



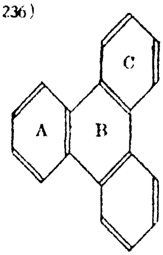
Pyrene (237)



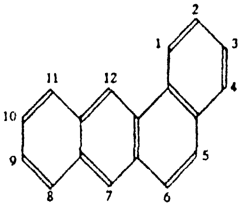
Benzanthrene (238)



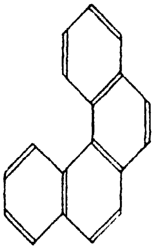
Chrysene (239)



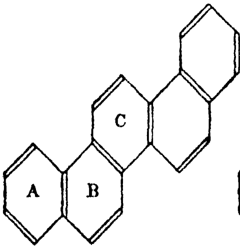
Triphenylene (240)



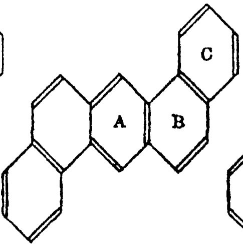
1,2 Benzanthracene (241)



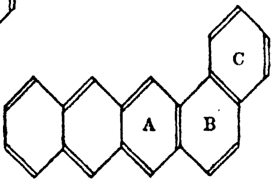
3,4 Benzphenanthrene (242)



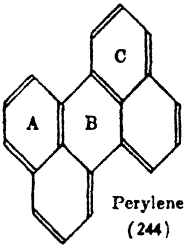
Picene (243)



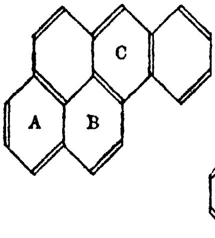
1,2,5,6-Dibenzanthracene



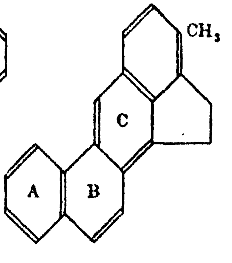
1,2,6,7-Dibenzanthracene



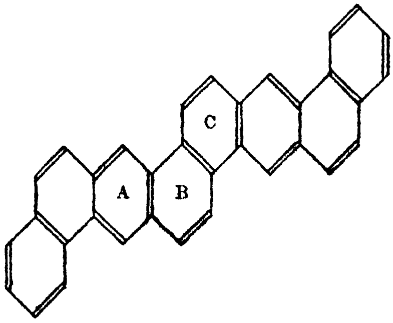
Perylene (244)



1,2-Benzpyrene



Methylcholanthrene



(6,7) 1',2'-naphtho (1,2) 1' 2'-phenanthra-phenanthrene

The formulæ above indicate the main types of condensed nuclei, and although many of them are not named as such, nearly all may be regarded as derivatives of phenanthrene, a conception which aids the memory considerably. Thus, of the substances displayed in formulæ above the first twelve may be classified as follows :—

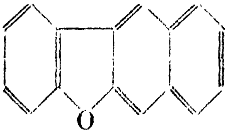
TABLE XXXI

		Usual Name.
Class I.	1, 2-Benzphenanthrene	Chrysene
	3, 4-Benzphenanthrene	
	4, 5-Benzphenanthrene	Pyrene
	6, 7-Benzphenanthrene	1, 2-Benzanthracene
	9, 10-Benzphenanthrene	Triphenylene
Class II.	1, 2, [1′-2′-Naphtha]phenanthrene	Picene
	6, 7 [1′, 2′-Naphtha]phenanthrene	1, 2, 5, 6-Dibenzanthracene
	6, 7 [2′, 3′-Naphtha]phenanthrene	1, 2, 6, 7-Dibenzanthracene
Class III.	4, 5-Methylenephenanthrene	Phenanthrenylmethane
	8, 9 ; 1, 10-Dibenzphenanthrene	Perylene
	1, 2 ; 4, 5-Dibenzphenanthrene	1, 2-Benzpyrene
Benzanthrene forms a class of its own, discussed below		

Whilst the above nomenclature is not strictly conventional or logical, it serves a useful purpose. Below are appended some notes on the various hydrocarbons.

Phenanthrenylmethane (4, 5-Methylenephenanthrene), isolated by Kruber [1] from the purified non-basic fraction of anthracene oil. If this be treated with sodium under reflux whilst a stream of carbon dioxide is passed, it is converted to the sodium salt of its 11-carboxylic acid which separates. The hydrocarbon itself may then be obtained from the purified acid by heat, and forms large plates, m. 116°.

Pyrene.—Pyrene is isolated from coal-tar in small quantities, and is a commercial article in the U.S.A., where the practical grade has a setting point of 145° and contains about 92 per cent. of pyrene.[2] Pure pyrene melts at 156°, and is exceptionally difficult to obtain pure, since traces of colourless brazan (245) and yellow 1, 2-benznaphthacene (246) persistently follow it through its purification. They can be removed by chromatographic adsorption. Oxidation of pyrene gives the 1, 6-pyrene-quinone (247), and in general pyrene is more reactive than phenanthrene, to which it has but a superficial resemblance. Reduction gives mainly the 1, 2, 3, 6, 7, 8-hexahydropyrene ; [3] substitution takes place largely at the ' 1 ' position.



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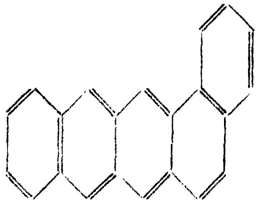

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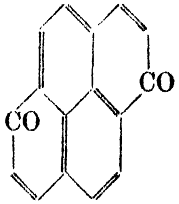

(247)

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[1] Kruber, *Ber.*, 1934, **67**, 1000.

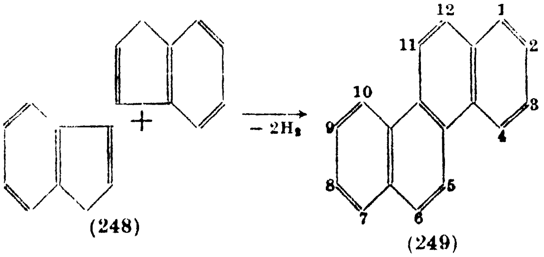
[2] Vollmann, Becker, Corell and Streeck, *Ann.*, 1937, **531**, 1. A comprehensive survey of the chemistry of pyrene.

[3] Cook and Hewett, *J.C.S.*, 1933, **398**.

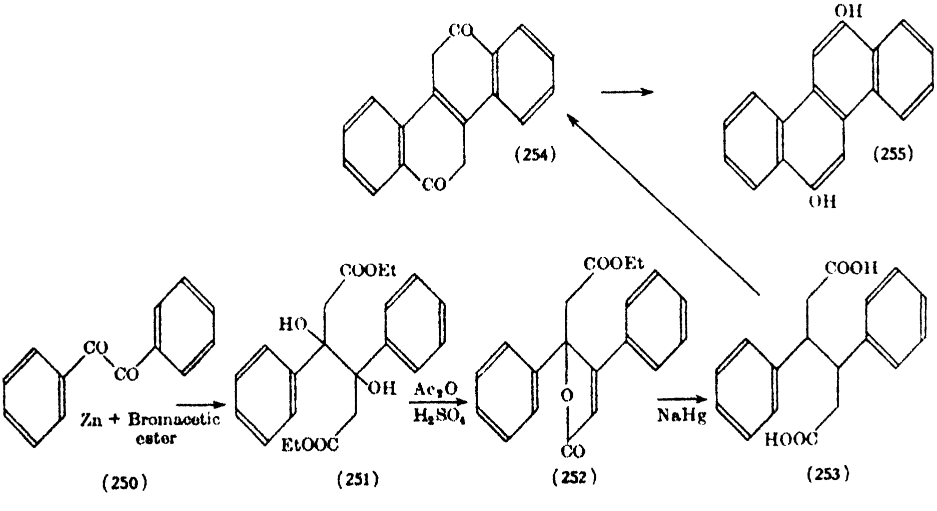
Benzanthrene.—The benzanthrene obtained by reduction of benzanthrone (*q.v.*) is only superficially related to phenanthrene, as it carries a methylene group in what could have been the ' 9 ' position of the phenanthrene structure. Benzanthrene is seldom met with, and has no outstanding properties.

Chrysene.—This hydrocarbon, $C_{18}H_{12}$, is found in the higher fractions of tar, and in the solid products of nearly all pyrogenic reactions involving aromatic hydrocarbons. It was originally called chrysene because of its supposedly yellow colour, which was shown by Liebermann,[1] as long ago as 1871, to be due to an impurity, whilst Schmidt accidentally obtained a colourless sample of chrysene in an investigation of a so-called nitro-anthracene.[2] Purification of chrysene by chromatographic adsorption rapidly removes the coloured material.[3]

Synthetic reactions in the chrysene field are of exceptional interest, and it is a striking fact that the method of preparing chrysene devised fifty years ago by Spilker [4] is now the standard method of manufacture of chrysene (249) for industrial purposes. Spilker's method [4] involves the passage of indene vapour through a red hot tube, and if care be taken to use sulphur-free indene (248), the yield amounts to 70 per cent. of the indene used.



The laborious synthesis of Beschke [5] has the advantage of producing derivatives of known structure, which have value as reference compounds in orientating chrysene compounds. The first stage in Beschke's synthesis is the preparation of 3, 4-diaryl substituted derivatives of hexene-3-diacid-1, 6. These can then be cyclised to 6, 12-dihydroxychrysene derivatives by concentrated sulphuric acid and acetic anhydride (254 and 255), e.g.



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[1] Liebermann, *Ann.*, 1871, **158**, 299.

[2] Schmidt, *J. Pr. Chem.*, 1874, **9**, 241.

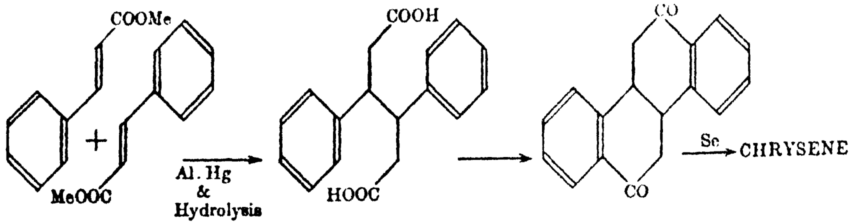
[3] Winterstein, Schön and Vetter, *Z. Physiol. Chem.*, 1934, **230**, 158.

[4] Spilker, *Ber.*, 1893, **26**, 1538.

[5] Beschke, *Ann.*, 1911, **384**, 143.

The production of the correct intermediate for this synthesis is achieved by commencing with benzil (250) or its derivatives, which react with bromacetic ester and zinc in the Reformatsky reaction to give substituted hexane-diol-diacid esters (251). With acetic anhydride and sulphuric acid, these yield unsaturated lactones (252) which, on reduction with sodium amalgam, are converted to the desired intermediates (253).

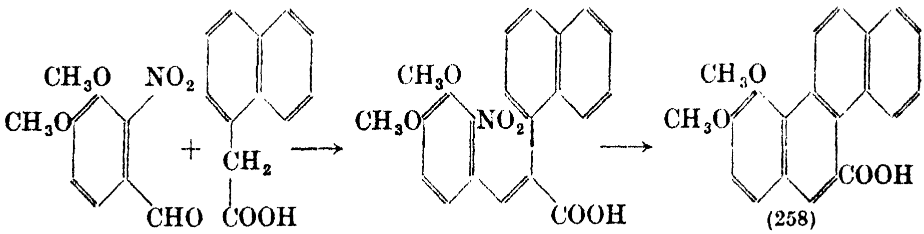
It will readily be appreciated that the chrysene synthesis just described is merely typical of a series of reactions involving diaryl substituted adipic acids which can be made to give chrysene or its derivatives; indeed, in the synthesis of Braun and Irmisch,[1] a diphenyl adipic acid itself (257) was obtained by aluminium amalgam reduction of cinnamic ester (256) followed by hydrolysis,



(256) (257) (258)

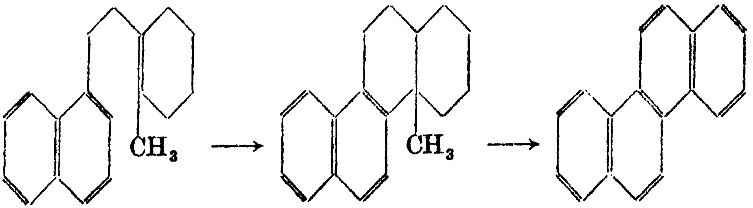
and gave on cyclisation, diketohexahydrochrysene (258), which could be converted by reduction of the carbonyl groups and selenium dehydrogenation to chrysene itself.

It will, of course, be obvious that many of the synthetic methods used for the production of phenanthrene derivatives may be extended to the synthesis of chrysene compounds by substitution of a naphthalene derivative for one of the aromatic components. Thus, in Pschorr's method, the following reactions may be visualised :—



(258)

leading to dimethoxychrysene carboxylic acid (258) which can readily be decarboxylated to dimethoxychrysene. An interesting synthesis of chrysene is that of Cook,[2] in which 1-naphthyl-2(2-methyl *cyclo*hexenyl)ethane (259) is



(259) (260) (261)

converted by cyclisation to methyl octahydrochrysene (260) from which it is possible to obtain chrysene (261) by selenium dehydrogenation. It should be noted that angular methyl groups are removed during aromatisation with selenium.

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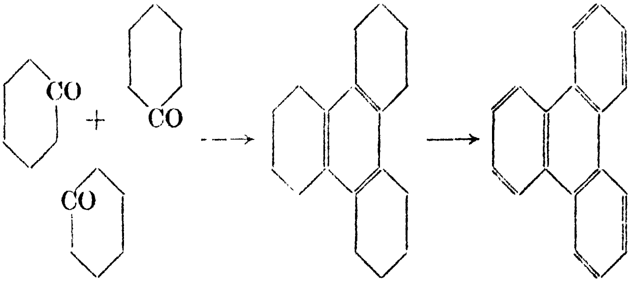
[1] Braun and Irmisch, *Ber.*, 1931, **64**, 2461.

[2] Cook *et al.*, *J.C.S.*, 1934, 653 and 1727; 1935, 667.

Chrysene forms small plates, colourless when pure, but often tinged yellow, m. 251°, b. 453°; it readily gives 5, 6-chrysenequinone on chromic oxidation and is of interest in that it is found as a dehydrogenation product of cholesterol and sterols (see Chap. X).

Triphenylene.—This hydrocarbon was so named because it can be regarded structurally as an assemblage of three *o*-phenylene groups. Kaffer[1] first found triphenylene in crude coal-tar chrysene, and it was prepared by Mannich,[2] who treated cyclohexanone with strong sulphuric acid, a triple condensation taking place which is analogous to the formation of mesitylene from acetone, or triphenylbenzene from acetophenone. The product is dodecahydrotriphenylene (262), which is dehydrogenated smoothly to triphenylene by selenium (263). Even in 1863 mention of the thermal decomposition of benzene to more complex hydrocarbons was discussed in "Watt's Dictionary", and three years later Berthelot[3] published data on the subject. He isolated, among others, a C_{18} hydrocarbon 'melting about 200°'; Berthelot called it 'chrysene'. The same hydrocarbon was obtained by Schultz[4] from bromobenzene and sodium, and the identity of the two hydrocarbons was the subject of a dispute between these workers. Mannich finally showed the identity of the hydrocarbon obtained by Berthelot's pyrolytic method, with pure synthetic triphenylene.

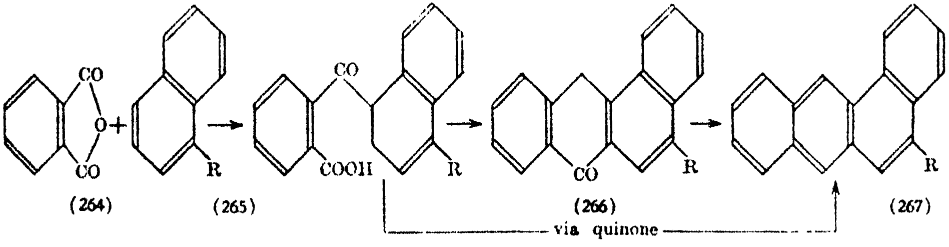


(262) (263)

Triphenylene forms large white crystals, m. 199°, and does not give a simple quinone on oxidation as do the other members of this series, since it lacks carbon atoms analogous to the 9–10 carbons of phenanthrene.

1, 2-Benzanthracene.—The chief interest of this substance lies in its historical importance in connexion with the study of carcinogenic hydrocarbons (*q.v.*). The synthesis of 1, 2-benzanthracene and its derivatives is effected by one of the methods below, many of which have been elaborated by Cook and his co-workers in this country, and by Fieser in America.

(1) *The Phthalic Anhydride Method*.[5]—This is a modified Friedel and Crafts reaction between phthalic anhydride and an α-substituted naphthalene (264), which gives first a ketonic acid (265); the keto group is



(264) (265) (266) (267)

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[1] Kaffer, *Ber.*, 1935, **18**, 1912.

[2] Mannich, *ibid.*, 1907, **40**, 153.

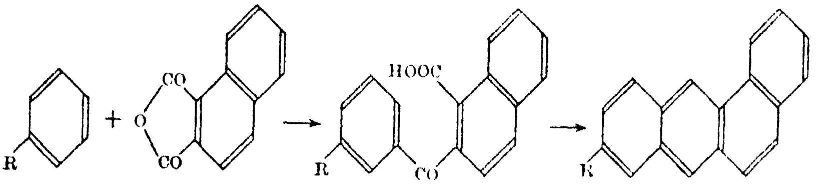
[3] Berthelot, *Ann.*, 1867, **142**, 254; *Bull. Soc. Chim.*, 1867 (2), **7**, 274.

[4] Schultz, *Ber.*, 1876, **9**, 547.

[5] Cook, *J.C.S.*, 1930, 1087; 1932, 456 and 1472. Fieser, *J.A.C.S.*, 1933, **55**, 3342.

reduced to methylene and the compound ring closed to an anthrone analogue (266), which reduces quite readily to the hydrocarbon (267). In some cases it is possible to annulate the keto acid direct to a quinone and then reduce this to the substituted 1, 2-benzanthracene, but this method will not work with highly substituted naphthalene derivatives or acenaphthenes.

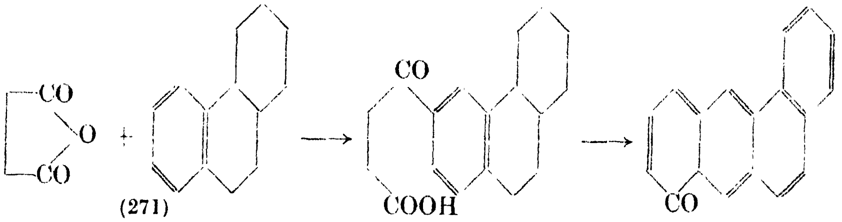
(2) A variant of the method above is to react an alkyl benzene with the



(268) (269) (270)

naphthalene analogue of phthalic anhydride (268). The remainder of the synthesis will be obvious from the formulæ (269) and (270). It should be noted, however, that the primary condensation can occur in two ways leading to the '6' and '7' alkyl 1, 2-benzanthracenes.

(3) Another modification of Haworth's succinic anhydride synthesis, due to Cook[1] is the condensation of octahydrophenanthrene (271) with succinic anhydride to give the keto acid (272) which may be reduced and an-

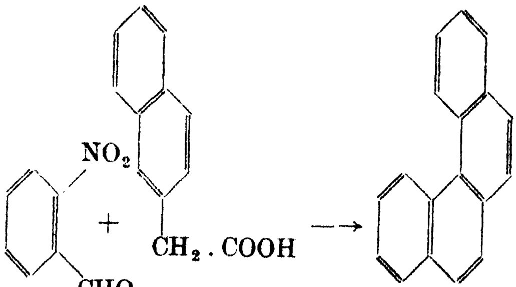


(271) (272) (273)

nulised to (273) in the presence of dehydrating agents. By dehydrogenation, the benzanthracene derivative itself may be obtained, albeit in very small yield.

3, 4-Benzphenanthrene.—This hydrocarbon is of interest as being the simplest substance yet shown to have carcinogenic properties. Two methods of synthesis are valuable in preparing this hydrocarbon and its derivatives.

(1) An extension of Pschorr's method,[2] in which *o*-nitrobenzaldehyde (274)



(274) (275)

and β-naphthylacetic acid are the starting materials and 3, 4-benzphenanthrene, the final product (275).

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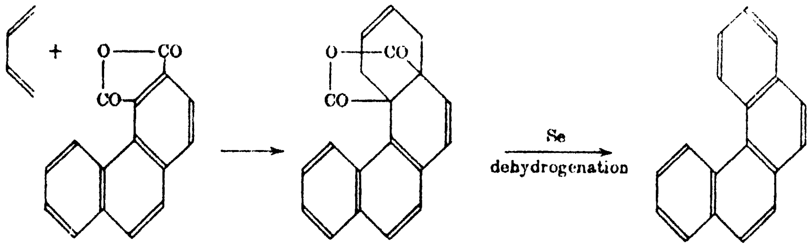
[1] Cook and Haslewood, *J.C.S.*, 1935, 767.

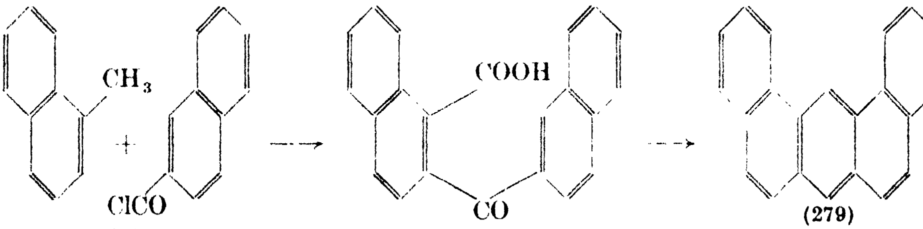
[2] Cook, *ibid.*, 1931, 2524.

(2) The second method constitutes an ingenious adaptation of the Diels-Alder synthesis.[1] This involves the addition of butadiene to the acid anhydride (276) and dehydrogenation of the product to 3, 4-benzphenanthrene.



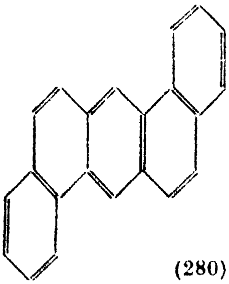
(276)

The Dibenzanthracenes.—Of these, the 1, 2, 5, 6- and 1, 2, 6, 7-isomers are important because of their carcinogenic properties (see Chap. XI), and are conveniently discussed in connexion with the two previous hydrocarbons. Cook,[2] in 1932, prepared 1, 2, 7, 8-dibenzanthracene by a modification of the phthalic anhydride method. Thus, when α-methylnaphthalene is subjected to a Friedel and Crafts reaction with β-naphthoyl chloride (277) a ketone is obtained which can be oxidised to the carboxylic acid (278). This annulates to the quinone of 1, 2, 7, 8-dibenzanthracene (279), which can be obtained from it by reduction. The method of annulation is by the following steps :—

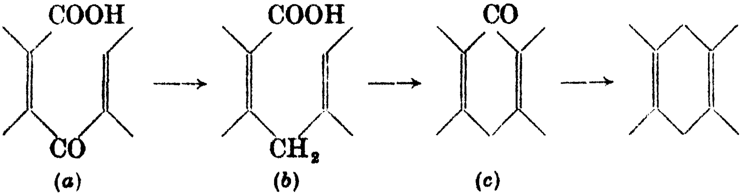


(277) (278) (279)

(*a*) Reduction of the keto acid at the carbonyl group.
(*b*) Annulation to the anthrone.
(*c*) Reduction, thus :—



(280)



(*a*) (*b*) (*c*)

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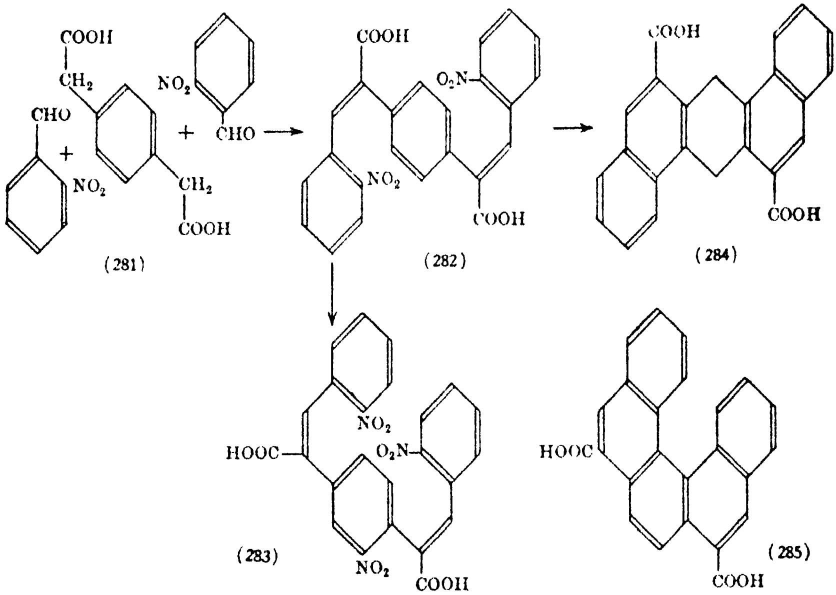
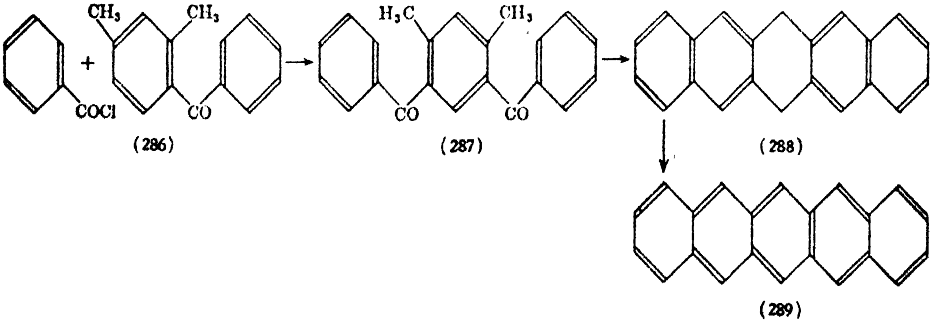
[1] Fieser and Herschberg, *J.A.C.S.*, 1935, **57**, 1508 and 2192.

[2] Cook, *J.C.S.*, 1932, 1472.

If the keto group be not reduced before ring closure, and an attempt is made to obtain the corresponding dibenzanthraquinone, a molecular rearrangement takes place and the quinone of 1, 2, 5, 6 dibenzanthracene is obtained (280). An interesting application of Pschorr's method[1] in this field is the use of phenylene diacetic acid (281) in condensation with o-nitrobenzaldehyde. The complex dinitro acid formed can be written in two ways (282) and (283) showing how, on annulation, it gives rise not only to 1, 2, 5, 6 dibenzanthracene dicarboxylic acid (284), but also to the dibenzphenanthrene dicarboxylic acid (285), both of which can readily be decarboxylated to their respective hydrocarbons.



Easily the best method of making 1, 2, 5, 6 dibenzanthracene is the condensation of β-methylnaphthalene and β-naphthoylchloride and pyrolysis of the ketone so obtained when a 30 per cent. yield of the dibenzanthracene is obtained by simple loss of water.[2] One most peculiar dibenzanthracene is the linear hydrocarbon—2, 3, 6, 7 dibenzanthracene. Clar[3] and his co-workers prepared the starting material—a diketone (287) by the action of benzoyl chloride and anhydrous aluminium chloride on m-xylylphenyl ketone (286). Annulation of this ketone was effected by pyrolysis in the manner just described for 1, 2, 5, 6



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[1] Weitzenböck and Klinger, *Monatsch*, 1918, **39**, 315.

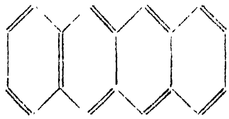
[2] Clar, *Ber.*, 1929, **62**, 350 and 1378 ; Fieser and Dietz, *ibid.*, 1929, **62**, 1827.

[3] Clar and John, *ibid.*, 1929, **62**, 3021 ; 1930, **63**, 2967.

dibenzanthracene and a dihydro-2, 3, 6, 7-dibenzanthracene was obtained (288) which on dehydrogenation gave 2, 3, 6, 7-dibenzanthracene, a deep blue hydrocarbon of extraordinary reactivity. (See also Vol. III, Chap. VI.)

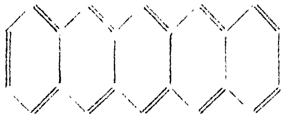
The colour of this substance is in keeping with the gradual increase in absorption in the visible spectrum shown by linear benzenoid aggregates. Thus, we have

Naphthacene



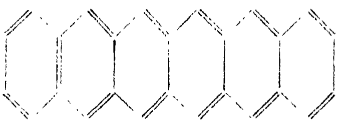
red

Pentacene (dibenzanthracene)



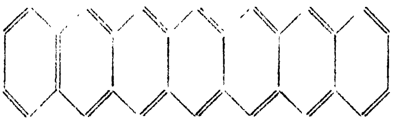
blue

Hexacene



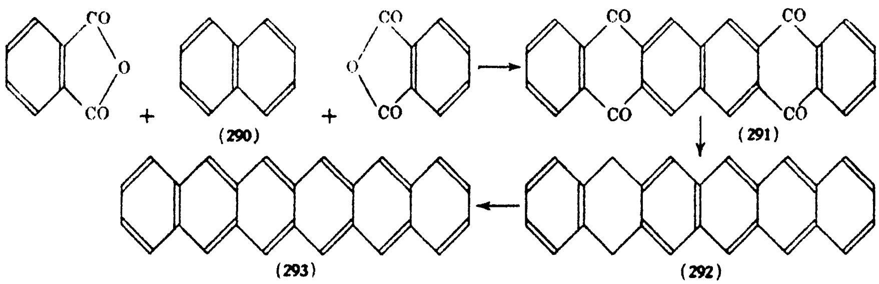
blue-green

Heptacene



green-black

By utilising the benzologs of the starting materials just discussed, it was possible for Marschalk[1] to obtain dihydrohexacene and dihydroheptacene, in which molecules the piling up of *ortho*-quinonoid rings leads to visible colour, the former being orange and the latter violet. Clar[2] obtained hexacene, a deep green crystalline hydrocarbon, by condensing phthalic anhydride and 1, 5-dihydroxynaphthalene (290) to give the dihydroxytetraketohexacene (291) which is readily reduced by fusion with zinc chloride, zinc dust and sodium



chloride to dihydrohexacene (292) identical with Marschalk's compound; further dehydrogenation to hexacene (293) is carried out by sublimation with copper powder. Clar[3] has also obtained heptacene as a black-green crystalline solid.

Picene, $C_{22}H_{14}$, was originally isolated from the higher boiling fractions of coal and lignite tars,[4] and later from petroleum pitch from Californian crudes.[5] It has also been obtained by the degradation of cholic acid and cholesterol structures.[6] The first synthesis was that of Lespieau,[7] who heated naphthalene and ethylene dibromide with anhydrous aluminium chloride (294). This method was repeated by Ruzicka many years later, the intermediate di-(1-naphthyl)ethane (295) being isolated. Ruzicka and Hosli [1] also devised an alternative route in which the Grignard reagent from α-naphthylethyl-chloride is allowed to react with α-tetralone (296), giving an alcohol which readily loses water to form α[1-naphthyl]-β[3, 4-dihydro-1-naphthyl] ethane (297), which can be annulated to picene (298). Hirn [2] also obtained picene by pyrolysing α-dinaphthostilbene (299).

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[1] Marschalk, *Bull. Soc. Chim.*, 1939, **6**, 1112.

[2] Clar, *Ber.*, 1939, **72**, 1817.

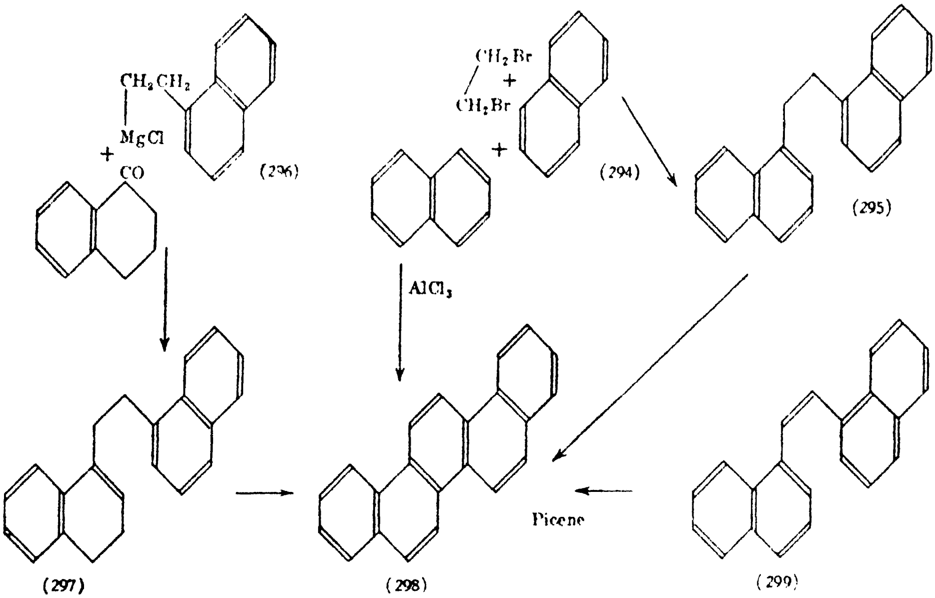
[3] Clar, *ibid.*, 1942, **75**, 1330.

[4] Burg, *ibid.*, 1880, **13**, 1834.

[5] Graebe and Walter, *ibid.*, 1881, **14**, 175.

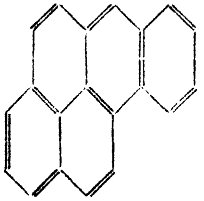
[6] Ruzicka *et al.*, *H. Ch. Acta*, 1934, **17**, 200

[7] Lespieau, *Bull. Soc. Chim.*, 1883, [3], **37**, 6; 238.

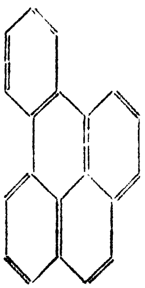


Picene forms beautiful white plates, with a blue fluorescence, m.p. 365°; its boiling point, 520° C., is the highest of any known assemblage of benzene rings.

Benzpyrene.



1, 2-Benzpyrene



4, 5-Benzpyrene

The structures of the two benzpyrenes commonly met with are given above. The 1, 2-isomer is of considerable interest as being the substance isolated by Cook and his co-workers [3] from pitch, of which it is an active carcinogenic component. Two tons of pitch gave sufficient 1, 2-benzpyrene to serve for identification purposes, the amount indicating that the amount actually present in pitch is equivalent to 30 mg. per kilo. The preparation of 1, 2-benzpyrene has been carried out by Cook and Hewett,[1] using an extension of the Haworth succinic anhydride condensation. The procedure described below is that of Fieser[2] and his co-workers, which, although essentially the same as that of Cook and Hewett, gives improved yields. Pyrene (300) is condensed with succinic anhydride in nitrobenzene solution, in the presence of anhydrous aluminium chloride to give 4-pyrenylbutanone-4-acid-1 (301) which is reduced

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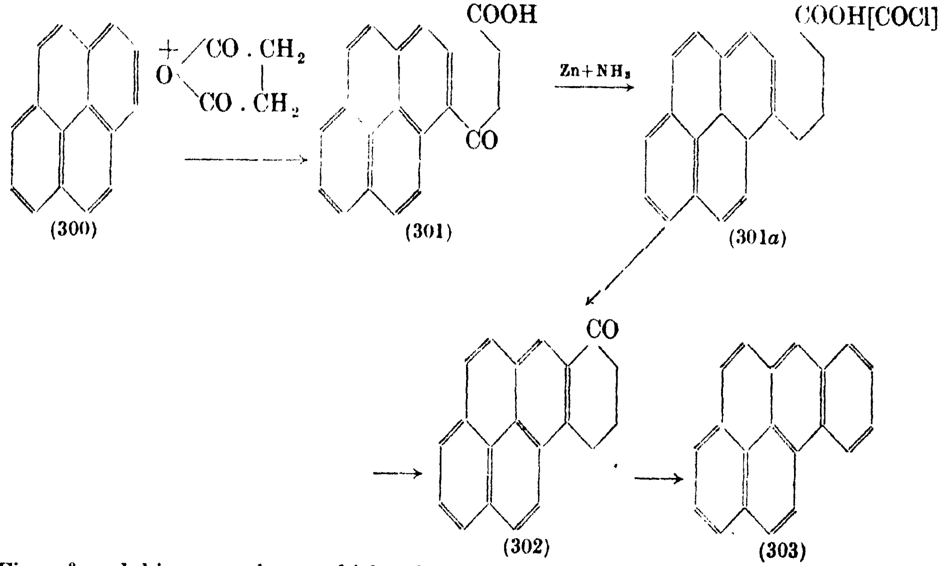
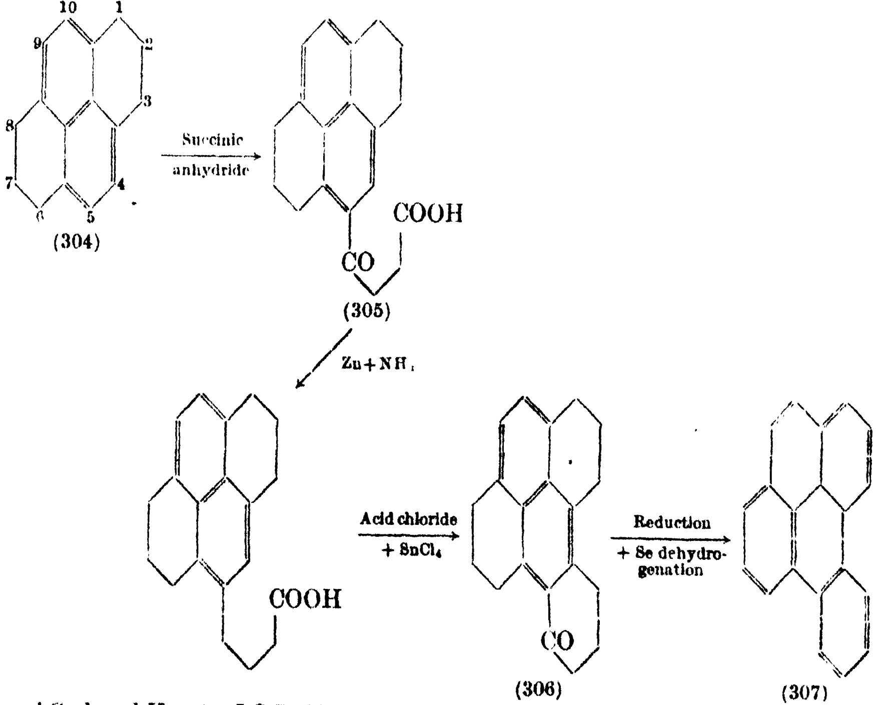
[1] Ruzicka and Hosli, *H. Ch. Acta*, 1934, **17**, 470.

[2] Hirn, *Ber.*, 1899, **32**, 3341.

[3] Cook and Hewett and Hilger, *J.C.S.*, 1933, 395.





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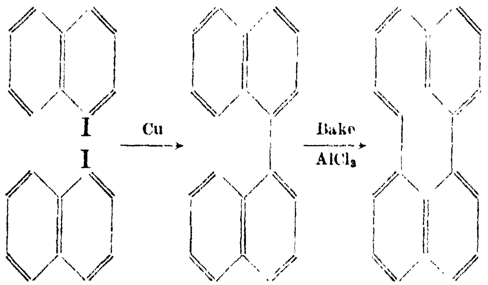
[1] Cook and Hewett, *J.C.S.*, 1933, 398.

[2] Fieser, *J.A.C.S.*, 1935, **57**, 782 ; Winterstein, Vetter and Schon, *Ber.*, 1935, **68**, 1079.

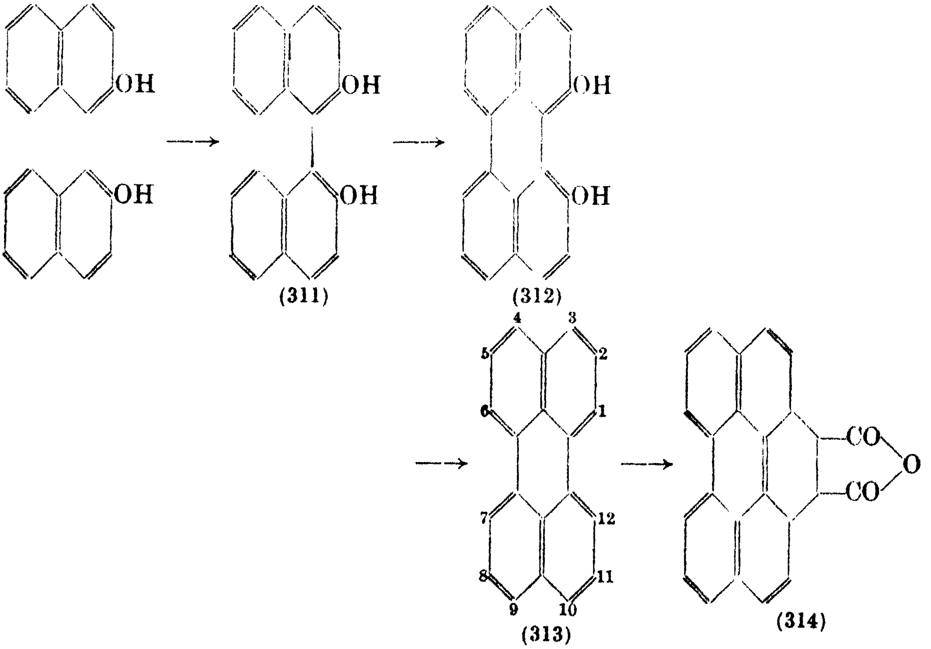
by zinc and ammonia to 4-pyrenylbutane acid (301*a*). This acid is converted to the chloride and annulated with stannic chloride to ketotetrahydro-1, 2-benzpyrene (302). This can be dehydrogenated direct to benzpyrene but the yield is poor, and it is preferable to hydrogenate under pressure to convert the keto-compound to tetrahydrobenzpyrene, which is dehydrogenated to benzpyrene itself (303) by selenium.

The preparation of the 4, 5-benzpyrene is an excellent example of the use of a partially hydrogenated starting point in order to induce ring-formation in a different direction. Cook and Hewett,[1] in this case, started with hexahydropyrene (304), and carried through a series of reactions similar to those already described for 1, 2-benzpyrene. In this case annulation can only take place in the 4, 5, or 9, 10-positions (which are equivalent) leading to the formation of 4, 5-benzpyrene (plates ; m. 177°) according to the formulæ (305 to 307).

Perylene.—Although perylene, $C_{20}H_{12}$, occurs in coal-tar, and has been isolated therefrom,[2] it was first obtained by synthesis [3] from naphthalene and anhydrous aluminium chloride. This method, however, gives no indication of its structure. If α-iodonaphthalene (308) is heated with copper bronze, αα′-dinaphthyl (309) is readily formed. This, on baking with dry aluminium chloride,



(308) (309) (310)



(311) (312) (313) (314)

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[1] Cook and Hewett, *J.C.S.*, 1935, 767.

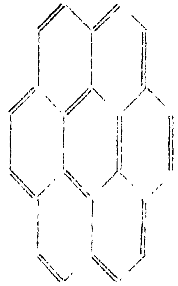
[2] Cook, Hewett and Hilger, *ibid.*, 1933, **395**.

[3] Scholl, Seer and Weitzenböck, 1910, **43**, 2202 (see also *Ann.*, 1912, **394**, 11 ; 1913, **398**, 2 ; *Ber.*, 1921, **54**, 109.

gives a moderate yield of perylene (310). Scholl called it perylene from 'peri-di-naphthylene'. The yield by this process is only a few per cent. The synthesis by which perylene is obtained for research purposes is that of Zinke[1] (to whom we owe much of our knowledge of perylene derivatives). When β-naphthol is treated with ferric chloride it readily yields the dinaphthol (311). This, on heating with phosphorus trichloride, gives some dinaphthylene oxide and perylene (313), presumably *via* the 1, 12-dihydroxy compound (312).

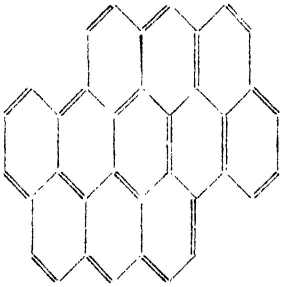
Perylene forms brilliant yellow leaflets, m. 265°, subliming at 350–400°. It is reduced by hydriodic acid and red phosphorus to the 1, 2, 3, 7, 8, 9-hexahydro compound,[2] m. 183°. It also condenses with maleic anhydride through the 1, 12-diene structure,[3] giving the product (314). Perylene halogenates, nitrates and sulphonates normally, substituents entering the 3, 9, 4, 10 positions in that order, which appears to be the logical outcome of its relation to naphthalene.

There are many other complex fused ring derivatives of benzene; some, such as retene, fichtelite and methylcholanthrene, are discussed in their proper sphere, that of the polyterpenes; others have an interest in that they mark some peculiar point in the structural development of the group. An example of the latter is coronene (315), so-called because the six benzene rings form a corona or wreath about the central ring. It was first prepared in 1932.[4] It is interesting to note also that dinaphtho-coronene (316) has also been prepared.



(315)

$C_{24}H_{12}$
yellow needles
m. 429–430°



(316)

$C_{36}H_{15}$

POLYNUCLEAR HYDROCARBONS CONTAINING TWO OR MORE RINGS DIRECTLY LINKED

Diphenyl, $C_{12}H_{10}$, appears first to have been recognised by Fittig,[5] who obtained it by the action of sodium on bromobenzene in ether. It was shortly afterwards prepared by Berthelot[6] by passing the vapour of benzene through a red-hot tube packed with fragments of hard glass; it is by this process that diphenyl is produced industrially to-day. Diphenyl appears to be an almost universal concomitant of pyrolytic reactions involving aromatic hydrocarbons, but numerous reactions not of a pyrolytic nature have been shown to produce it. Some typical examples are :—

(1) Ullmann's method,[7] in which iodobenzene is heated with copper powder for several hours at 210–230°. The yield is about 60 per cent. of the theoretical figure, but the method has the advantage of being general, and of working when the aromatic group contains substituents. Thus, di-*m*-tolyl (317) can be

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[1] Zinke and Hausing, *Monatsch.*, 1920, **40**, 403.

[2] Zinke and Unterkreuter, *ibid.*, 1934, **44**, 365.

[3] Clar, *Ber.*, 1932, **65**, 1932.

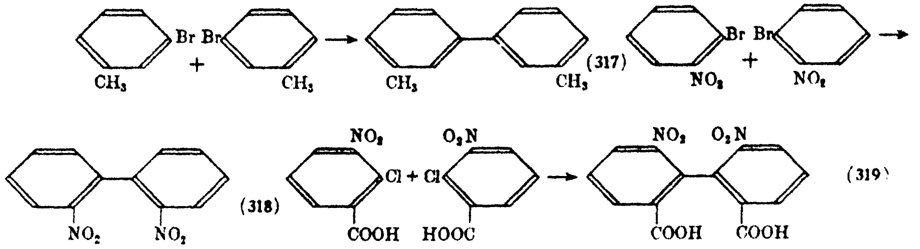
[4] Scholl, Meyer *et al.*, 1932, **65B**, 902.

[5] Fittig, *Ann.*, 1862, **121**, 361.

[6] Berthelot, *ibid.*, 1867, **142**, 252.

[7] Ullmann, *ibid.*, 1904, **332**, 38.

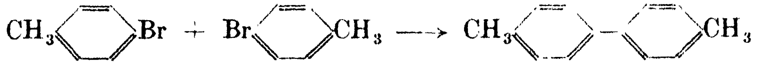
obtained from 3-bromotoluene ; 2, 2′-dinitrodiphenyl (318) from *o*-bromonitrobenzene,[1] whilst Kenner and his co-workers have extended its use[2] to the diphenic acid derivatives, e.g., to 6, 6′-dinitrodiphenyl-2, 2′-dicarboxylic acid (319).



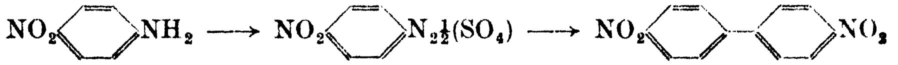
(317) (318) (319)

Extension of the method to naphthalene derivatives has also proved successful, e.g., the production of dinaphthyl for research in the perylene group (see p. 187), and for the production of linear polyphenyls.[3]

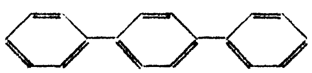
(2) Krizewsky and Turner[4] have devised a method by which good yields of diphenyl derivatives may be obtained in cases where Ullmann's[5] method is unsatisfactory. The bromaryl compound (e.g., *p*-bromotoluene) is dissolved in ether and treated with anhydrous copper chloride ($CuCl_2$) and magnesium. A vigorous reaction sets in, presumably a Grignard reaction, and a good yield of di-*p*-tolyl is obtained :—



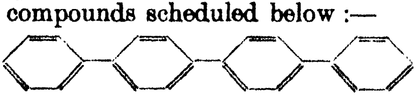
(3) Frequently in the diazotisation of arylamines and the attempted replacement of the diazo group by a halogen or cyano group, according to the method of Sandmeyer, the desired compound is obtained in very poor yield, and much of the material is converted to a diphenyl derivative. This is particularly true of nitro-amines, especially those with a nitro- group *meta-* to the amino group. The method[6] may be used for the preparation of diphenyl derivatives, and the yield is increased if the diazonium sulphate is formed and allowed to decompose in the presence of copper powder at 30–40°. The method is also particularly



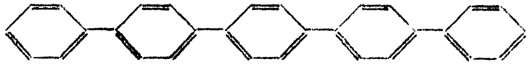
applicable to *β*-naphthylamine derivatives.[7] The method can be extended to yield the ter-, tetra- and penta-phenyls (often known as diphenylbenzene, didiphenyl and didiphenylbenzene[8] by carrying out the diazotisation of aniline sulphate in a mixture of acetic and sulphuric acid, using amyl nitrite, and by adding formic acid. Some diphenyl is produced, but the non-volatile insoluble residue is a mixture of the first three compounds scheduled below :—



Terphenyl, m. 205° b. 225/15 mm.
[diphenylbenzene]



Tetraphenyl, sublimes 180–230° in vac. 2 mm.
[didiphenyl]



Pentaphenyl, sublimes at 2 mm. at 285–290°
[didiphenylbenzene]

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[1] Ullmann and Bielecki, *Ber.*, 1901, **34**, 2176.

[2] Kenner and Stubbings, *J.C.S.*, 1921, **119**, 598 ; Kenner *et al.*, *ibid.*, 1923, **123**, 1949.

[3] Bowden, *ibid.*, 1931, 1113.

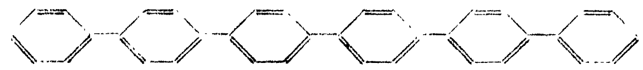
[4] Krizewsky and Turner, *ibid.*, 1919, **115**, 559.

[5] Ullmann, *Ann.*, 1904, **332**.

[6] Ullmann and Forgan, *Ber.*, 1901, **34**, 3802 ; Ullmann and Frentzel, *Ber.*, 1905, **38**, 725 ; Gattermann and Ehrhardt, *Ber.*, 1890, **23**, 1226.

[7] Chattaway, *J.C.S.*, 1895, **67**, 653.

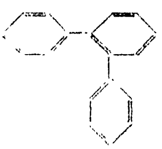
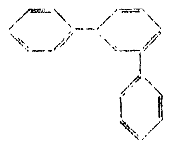
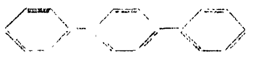
[8] Gerngross *et al.*, *Ber.*, 1924, **57**, 742 and 747.



Sexiphenyl, m.p., 475° under pressure
[didiphenyldiphenyl]
(320)

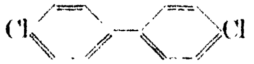
Pummerer and Bittner [1] obtained sexiphenyl (320) by heating iodoterphenyl with silver powder. The higher polyphenyls are of little interest at the moment, although the three terphenyls are industrially available in a tolerably pure form, the physical characteristics of which are given in the table below :—

TABLE XXXII

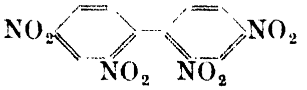
	 *o*-Terphenyl	 *m*-Terphenyl	 *p*-Terphenyl
Setting point	54°	83·85°	209–213°
Distillation range	330–350°	370–378°	381–388°
Density, 0°	1·14	1·164	1·236

Diphenyl itself forms large colourless plates, m. 70°, b. 254°, with a pleasant aromatic odour. It is extremely stable, and both in its crude state and partially chlorinated (to decrease its setting point) is used in chemical engineering as a heat transfer medium, e.g., for heating reaction vessels at temperatures of 150–220°.

In general, the chemical behaviour of diphenyl resembles that of benzene; it is readily chlorinated, nitrated and sulphonated and the substituents enter the *para*-positions symmetrically, giving the 4, 4′-disubstituted compounds,



(321)



(322)

e.g., 4, 4′-dichlorodiphenyl (321). Further, substituent groups enter the 2, 2′-positions as in 2, 2′, 4, 4′-tetranitrodiphenyl (322). It may be remarked here that the direct link between two aryl groups may be induced by a variety of modifications of the benzidine transformation which is virtually the isomerisation of a diaryl hydrazine to a diaminodiaryl. This transformation is discussed fully in the section on amines (Vol. II).

Consideration of the peculiar optical and geometrical isomerisms met with in the diphenyl and terphenyl sections is deferred to Chapter IV of Vol. III.

POLYAROMATIC HYDROCARBONS WITHOUT DIRECT INTRA-ARYL LINKAGE

The main classes of compound to be discussed in this section are :—

(1) The diaryl methanes.
(2) The triaryl methanes.
(3) The polyaryl ethanes.
(4) The stilbene family.

Diphenyl methane (323) is produced readily by the action of benzyl chloride on benzene in the presence of zinc or anhydrous aluminium chloride,[2] or of methylene chloride on benzene under similar conditions; by the action of sulphuric acid on a solution of dimethoxymethane[1] ('methylal') in benzene, or from benzyl alcohol and benzene under the influence of sulphuric acid.

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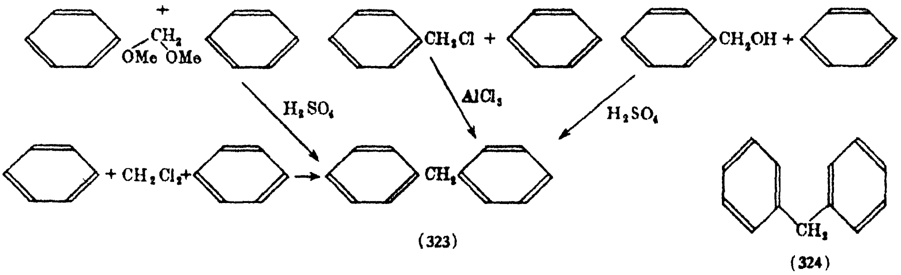
[1] Pummerer and Bittner, *Ber.*, 1924, **57**, 84.

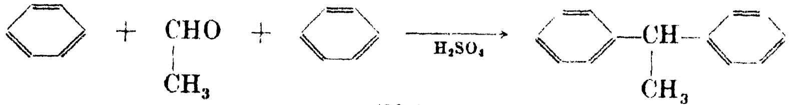
[2] Zincke, *Ann.*, **159**, 374.



(323)

(324)

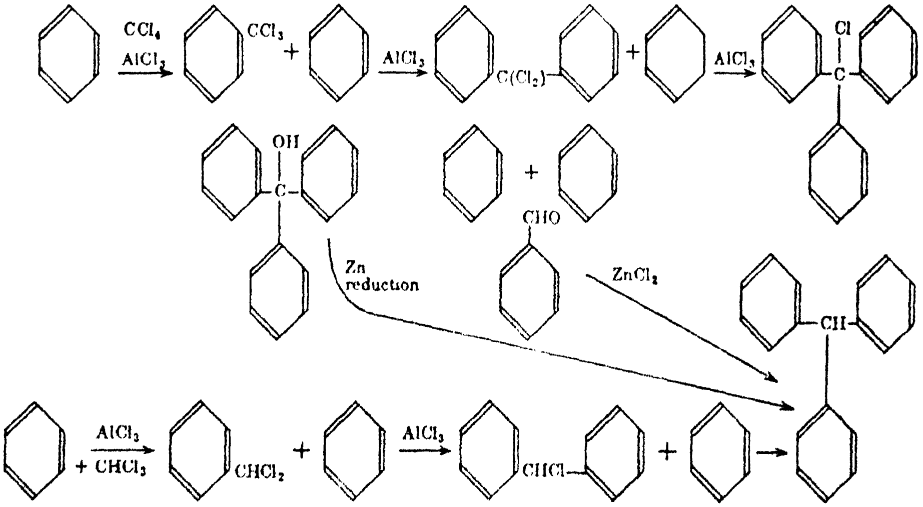
Diphenylmethane is a pleasant smelling liquid solidifying at 26–27°, and boiling at 262°. The hydrogens of the methylene group are intensely reactive, readily oxidised to the keto-group giving benzophenone, and replaceable by bromine. The methylene group will also condense with aldehyde groups and enter into a variety of reactions of a similar character; its structural analogy with fluorene is more apparent when the formula is written as (324). 1-1 Diphenylmethane (325), b. 286°, may be obtained by condensing acetaldehyde (conveniently in the form of paraldehyde) with benzene in the presence of sulphuric acid. It may also be prepared by Nieuwland's process, in which acetylene is passed into benzene containing anhydrous cuprous chloride. The reactions discussed above are to a wide extent general, and lead to a variety of nuclear substituted diphenyl derivatives, none of which, however, are of paramount importance.



(325)

TABLE XXXIII

THE FORMATION OF TRITANE



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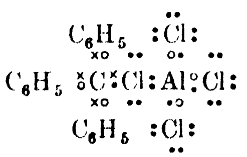
[1] Meyer, *Ber.*, 1873, 6, 963.

Triphenyl methane (often called 'tritane', whilst the triphenyl-methyl group is referred to as the 'trityl' group) is prepared by a variety of processes, chief amongst which is the interaction of carbon tetrachloride and benzene, or of chloroform and benzene, in the presence of anhydrous aluminium chloride. The use of chloroform [1] leads to the formation of some diphenylmethane; the use of carbon tetrachloride, the step-wise action of which may be followed, as shown in Table XXXIII, gives as the final product tritylchloride, which gives a firm compound with aluminium chloride of the structure :—



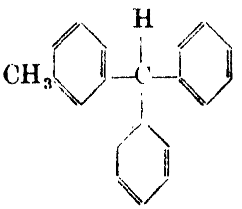
$$\begin{array}{lc} C_6H_5 & :\ddot{Cl}: \\ C_6H_5 & \overset{\times\circ}{\underset{\times\circ}{\circ}}C\overset{\times}{\underset{\times}{:}}Cl:Al\overset{\circ}{\underset{\circ}{:}}Cl: \\ C_6H_5 & :\underset{\cdot\cdot}{Cl}: \end{array}$$

which is analogous to the formula Al_2Cl_6. On decomposing this double compound with ether, the latter reacts chemically, giving triphenylmethane; this is the accepted laboratory procedure for obtaining the material which forms

$$[C_6H_5]_3CClAlCl_3 + [C_2H_5]_2O \longrightarrow [C_6H_5]_3CH + C_2H_5Cl + CH_3CHO + AlCl_3$$

large white crystals, m. 93°, b. 360°. The reactivity or lability of the methane hydrogen is, in this compound, remarkable, and governs its general behaviour. Thus any reagent capable of acting as an oxidising agent immediately oxidises triphenylmethane to the carbinol; attempts at reduction lead to complete breakdown of the molecule to benzene and toluene; indeed, the looseness of attachment of atoms such as those of the halogens to the methane carbon atom is such that they may readily be removed by reagents with the formation of 'free radicles' of the Gomberg or triphenylmethyl-type. The study of these is almost a branch of organic chemistry in itself, and is dealt with in detail in Chapter VIII, Vol. III.

The diphenyltolylmethanes are of interest in relation to the triphenylmethane groups of dyes. Thus, diphenyl-*m*-tolylmethane (326) has been obtained from



(326)

leucaniline, and serves to assist in elucidating the structure of that compound. It should be added that although tetraphenylmethane cannot be made by the continuance of the action of aluminium chloride on benzene and carbon tetrachloride, it can be made in small yield by reacting trityl chloride with phenylhydrazine or phenyl magnesium bromide (327).[2] Once prepared, tetraphenylmethane (328), m. 285°, b. 431° is a substance of exceptional stability, reacting not by splitting at the central carbon atom, but by substitution in the normal way into the phenyl nuclei. It has none of those peculiar properties which, when Gomberg went on to attempt the preparation of hexaphenylethane, led him to initiate the chemistry of free radicles.

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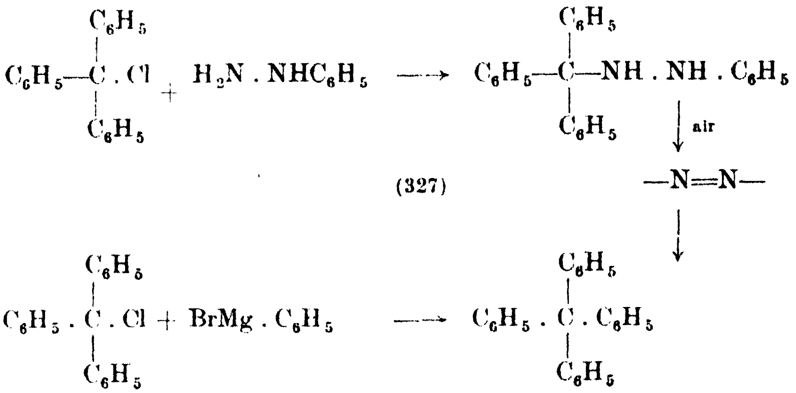
[1] Kekulé and Franchimont, *Ber.*, 1872, **5**, 906.

[2] Gomberg, *ibid.*, 1906, **39**, 1461.



$$C_6H_5-\overset{C_6H_5}{\underset{C_6H_5}{C}}\cdot Cl + H_2N\cdot NHC_6H_5 \longrightarrow C_6H_5-\overset{C_6H_5}{\underset{C_6H_5}{C}}-NH\cdot NH\cdot C_6H_5 \xrightarrow{\text{air}} -N{=}N- \longrightarrow$$

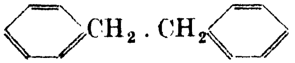
(327)

$$C_6H_5\cdot\overset{C_6H_5}{\underset{C_6H_5}{C}}\cdot Cl + BrMg\cdot C_6H_5 \longrightarrow C_6H_5\cdot\overset{C_6H_5}{\underset{C_6H_5}{C}}\cdot C_6H_5$$

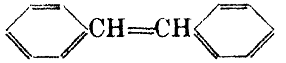
(328)

The Phenylethylenes and Related Compounds

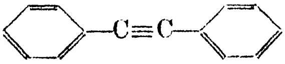
Styrene, phenyl ethylene, has already been discussed. The three compounds shown below are the prototypes of the main classes of hydrocarbon in this family.



Dibenzyl, diphenylethane
m. 53°, b. 284°

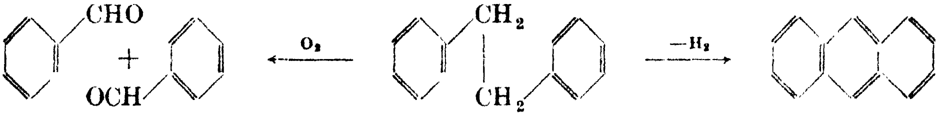


Stilbene, diphenylethylene
m. 125°, b. 307°



Tolane, diphenylacetylene
m. 60°

Dibenzyl, although it can be prepared by heating benzyl chloride with copper, is best prepared by the action of ethylene dichloride on benzene in the presence of anhydrous aluminium chloride. It forms very large white crystals with a persistent smell, somewhat reminiscent of hyacinths, on account of which, together with its resistance to alkali and cold oxidation, it is used in the perfuming of soap. Pyrolysis in a reducing atmosphere converts dibenzyl to



(329) (330)

anthracene (330) and mild oxidation leads to the formation of benzaldehyde (329).

Stilbene.—Was one of the earliest discovered hydrocarbons of this group, Williams[1] having obtained it in 1867 by the action of sodium on benzaldehyde. It is almost always in evidence when any compound of benzene, containing a single carbon in the side-chain, is submitted to pyrolysis. Thus, toluene passed over heated lead oxide gives stilbene;[2] a summary of such reactions is given in the table below.

It will be clear from the list shown, which is representative only, that stilbene must be a particularly stable structure. Stilbene forms lustrous white plates, of a peculiar odour, m. 125°, b. 307°; that usually obtained is the *trans*- form

---

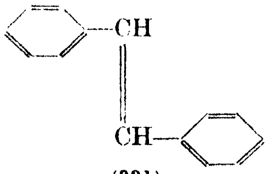
[1] Williams, *Zeit. fur Chem.*, 1867, 1432.

[2] Behr and Dorp, *Ber.*, 1873, **6**, 754.

TABLE XXXIV—SYNTHESES OF STILBENE

From—	Treatment	Reference
Benzyl sulphide	Pyrolysis	Laurent, Berzelius, *Jahres*, **25**, 616
Benzaldehyde	Heating with Na	Williams (Ref. 1, p. 192)
Benzaldehyde, sod. acetate and phenylacetic acid	Heat at 250°	Michael, *Am. Ch. J.*, 1879, **1**, 313
s-Diphenylethane	Chlorine	Kade, *J. Pr. Chim.*, 1879, 2, **19**, 465
s-Diphenylethane	Pyrolysis	Otto and Dreher, *Ann.*, 1870, **154**, 177
Benzoin	Heat with Zn dust	Limpricht, *Ann.*, 1870, **155**, 80
Toluene	Passed over hot litharge	Behr and Dorp (Ref. 2, p. 192)
Diphenylacetylene	Heat with HI and P at 173°	Barbier, *J.*, 1874, 421
Lead phenylacetate	Distillation with sulphur	Radiszewski, *Ber.*, 1873, **6**, 390
Thiobenzamide	Heat with Zn dust	Bamberger, *Ber.*, 1888, **21**, 55
Diphenyl cinnamate	Heat	Anschütz, *Ber.*, 1885, **18**, 1945
Diphenyldibromoethane	Alcoholic potash	Auwers, *Ber.*, 1891, **24**, 3308
Thiobenzaldehyde	Heat at 190°	Baumann and Klett, *Ber.*, 1891, **24**, 3308

(331); the *cis*- form has also been prepared (332) by the action of ultra-violet light on the *trans*- form; it is an oil, b.p. 142·3°-121 mm.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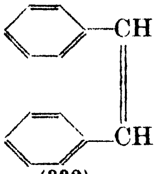
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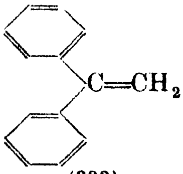
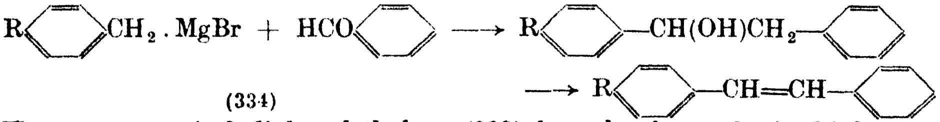
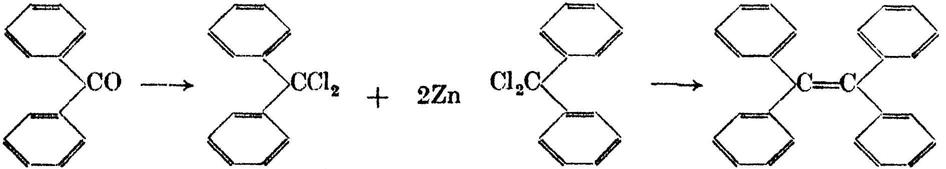

(333)

Stilbene adds halogens and hydrogen at the double bond in the usual way. Many stilbene derivatives are valued for their œstrogenic activity (*q.v.*), but these are not prepared direct from stilbene, many being prepared by a modification of the method of Hell and Meisenheimer in which a substituted benzyl magnesium bromide (334) is allowed to react on benzaldehyde, followed by distillation of the alcohol liberated by sulphuric acid :—



(334)

The unsymmetrical diphenylethylene (333) has also been obtained[1] by the action of alcoholic potash on 1, 1-diphenyl-2-chloroethane. Tetraphenyl ethylene (336), white crystals, m. 221°, b. 425°, may readily be prepared by converting benzophenone to its dichloride (335) and reacting the latter with zinc[2] or magnesium :—



(335) (336)

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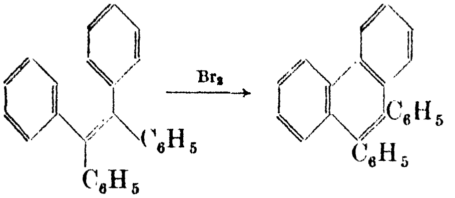
[1] Hepp, *Ber.*, 1874, **7**, 1409.

[2] Behr, *ibid.*, 1870, **3**, 751; 1872, **5**, 277.

In view of the accumulation of aryl groups round the ethylene link, it is interesting to note that tetraphenylethylene adds hydrogen and chlorine normally,[1] but does not add bromine—presumably owing to steric factors; with bromine there is formed 9, 10-diphenylphenanthrene—in fairly good yield[2] (337).



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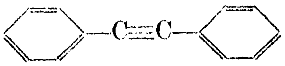
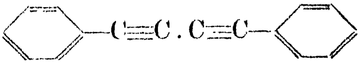


(338)



(339)

Diphenylacetylene (Tolan) (338).—This is quite a stable hydrocarbon, crystallising in large prisms, m. 62°, b. 300°, which may be distilled unchanged. The name 'Tolane' (dating back to its earliest preparation) is unsuitable, and in view of the reservation of the '-ane' termination for saturated hydrocarbons, should be discouraged. It may be prepared from dichlorodiphenylethane by the action of alcoholic potash.[3] In strong sulphuric acid at 60° it gives desoxybenzoin, and by oxidation that diphenyldiacetylene (m. 97°) which may also be obtained by oxidising the copper derivative of phenylacetylene by alkaline ferricyanides,[4] and is likewise a stable crystalline substance (339).

APPENDIX 1

SOME IMPORTANT REFERENCE WORKS ON HYDROCARBONS

(1) *Acyclic and Alicyclic Hydrocarbons*

K. **Alder.** "Die Methoden der Diene-synthese", 1933, Berlin

B. T. **Brooks,** "The Chemistry of Non-benzenoid Hydrocarbons", 1922, N. York.

G. **Egloff.** "Physical Constants of the Hydrocarbons", Vols. I and II, A.C.S. Monographs, 1939, N. York.

G. **Egloff.** "Reactions of Pure Hydrocarbons", A.C.S. Monograph, 1942, N. York.

G. **Egloff, Komarewsky** and **Hula.** "Isomerisation of Pure Hydrocarbons", A.C.S. Monograph, 1942, N. York.

C. **Ellis.** "The Chemistry of Petroleum Derivatives", 1934, N. York.

C. **Ellis.** "Hydrogenation of Organic Substances", 3rd Edn., 1930, N. York.

The Faraday Society. "Hydrocarbon Chemistry", 1939, London. A discussion reprinted from the *Transactions*.

D. **Holde.** "Kohlenwasserstofföle und Fette", 1933, Berlin.

J. P. **Laurie.** "Methane, its Production and Utilisation", 1940, London.

J. A. **Norton.** 'The Diels-Alder Synthesis', *C. Rev.*, 1942, **31**, 320.

(2) *Alicyclic Hydrocarbons*

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[2] Schoepfle and Ryan, *ibid.*, 1932, **54**, 3687.

[3] Limpricht *et al.*, *Ann.*, **145**, 347.

[4] Glaser, *ibid.*, **154**, 159.

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APPENDIX II

THE PETROLEUM INDUSTRY

Petroleum constitutes one of the most valuable chemical resources of the earth's crust. Quite apart from the fuel value of its products, petroleum (with which is included natural gas) is a storehouse of hydrocarbons from which can be made a vast variety of chemical substances of almost all types. Thus, not only aliphatic, but aromatic derivatives can be obtained by suitable manipulation of the raw material. In addition, natural gas may contain up to 1 per cent. of helium.

The petroleum industry may be conveniently divided into the following sections :—

1. Drilling, tapping and storing the crude.
2. Fractionating the crude.
3. Cracking, reforming and reconstituting.
4. Production of derived substances.

The two first sections, important and interesting as they are, cannot be considered within the scope of this book ; the mechanics of obtaining and storing the crude constitute important sections of applied geology and of hydraulic engineering ; fractionation of the crude material is a well-defined section of chemical engineering ; our first consideration must be the chemical nature of the crudes and the composition of the various fractions obtained.

The composition of natural gas is largely methane and ethane, with between 3 and 4 per cent. of propane and about half that quantity of butane ; on the other hand, cracked gas can be produced showing almost any desired composition of C_3 and C_4 hydrocarbons. Petroleum itself is classified according to the following constituents :—

Paraffins.—The simple, straight and branched chain members of the chemical family.

Aromatics.—The simple aromatic hydrocarbons.

Naphthenes.—Single and multiple rings of fully hydrogenated structure, mainly *cyclo*pentane and *cyclo*hexane homologues.

Asphalts.—High molecular weight hydrocarbons of a complex nature, low in hydrogen.

In addition, the asphaltic section often contains oxygenated members, and nearly all petroleums contain sulphur compounds. Contrary to general belief it is almost impossible to obtain pure hydrocarbons direct from petroleum by any simple process of distillation or crystallisation. Not only is the number of actual substances in the crude a large one, but innumerable constant boiling mixtures are formed which further complicate matters. To obtain individual chemical substances it is expedient to crack the higher boiling portions of petroleum and to isolate the C_2—C_6 hydrocarbons from the light cuts of the cracked product and to reform these to substances of known structure and purity.

The first separation carried out in the petroleum industry is distillation into three main fractions :—

1. Straight run gasolines.
2. Kerosenes.
3. Higher fractions.

It should be added that in the refiners' terminology ' gasolines ' includes all the light fractions up to 150°—although they may be stripped or ' cut ' into various subsidiary fractions, such as light petrol up to 70°, true gasoline 70–120°, and white spirit 120–150°. Straight run gasolines are largely lower paraffins with such aromatics and naphthenes as boil within the range of distillation. Reference has already been made to the presence of aromatics in petroleum (see p. 131) ; it may be added that straight run gasolines are of little value *per se*, and must be blended before they are of use as fuels for internal combustion engines. The proportion of such low boiling components in petroleum is small, and the following table shows the distribution of simple substances in an Oklahoma crude.[1]

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[1] Adapted from figures compiled by Washburn, *Ind. Eng. Chem.*, 1933, **28**, 891, 25.

TABLE XXXV

Hydrocarbons	B.P.	B.P. up to 100°	B.P. above 100°
		Per cent. present	Per cent. present
n-Hexane	68·7°	0·5	
2, 3-Dimethylbutane	58–58·3°	0·3	
2-Methylpentane	60·4–60·6°		
3-Methylpentane	63·2–63·3°		
n-Heptane	98·4°	0·9	
2, 2-Dimethylpentane	79·5°	0·03	
2-Methylhexane	89·67°	0·25	
3-Methylhexane	91·8°	Traces	
n-Octane	125·4°		1·0
2-Methylheptane	117·2°		0·16
n-Nonane	150·71°		1·0
n-Decane	174°		0·8
cyclo-Pentane		Traces	
Methyl*cyclo*pentane		0·2	
cyclo-Hexane	80·8	0·3	
Methyl*cyclo*hexane	100·8°	0·3	
1, 1-Dimethyl*cyclo*pentane	87·5°	0·03	
Nonanaphthenes	—	Traces	
Benzene	80·1°	0·08	
Toluene	112°	—	0·3
Xylenes	138–144°	—	0·28
Ethylbenzene	136·05°		0·03
Totals		2·89	3·57

From the figures given it will be seen that the total of these fractions only represents about 7 per cent. of the crude material. In addition, it must be added that there are unidentified low boiling constituents in crude oil giving in all about 20–25 per cent. of straight run gasolines.

Kerosenes, the next highest boiling fractions in the distillation of crude petroleum, represent the various cuts in distillation from 150–300° ; as with gasolines they may be subdivided according to the purpose for which they are to be used. Crude kerosene covering the whole range 150–300° may be cut for cracking later, or for Diesel fuel, or the earlier fractions may be used for solvents, the middle fractions for burning oils and the higher fractions reserved for Diesel fuel. The kerosenes represent some 40–50 per cent. of the crude, and have experienced various changes of industrial value. Thus, towards the end of last century they were of paramount value, the gasolines and higher fractions being merely waste products in the preparation of the kerosenes which were used as burning oils. The advent of the internal combustion engine raised the demand for and value of the gasoline and heavy lubricating fractions, leaving kerosene as an article of rapidly declining use and value, until to-day most of it is ‘ cracked ’ and ‘ reformed ’ to gasoline of high octane value. The recoil in value of kerosene is, however, becoming apparent again, since the wide advent of the Diesel engine and its adaptation in small units for road transport ; the demand for the heavier fractions for Diesel use has had its inevitable consequence in a hardening of kerosene values.

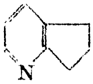
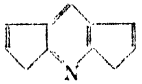
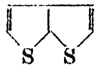
Kerosene from a chemical standpoint is an inextricable tangle ; it consists of hundreds of hydrocarbons present in comparatively small proportions, which are almost impossible to separate and characterise. Rough separations into aliphatic, naphthenic and aromatic can be carried out by taking into account the different physical and chemical properties of the groups, but no real ‘ analysis ’ of the kerosene (or higher fractions) has been made.

THE HIGHER PETROLEUM FRACTIONS

Vacuum distillation of the residue remaining after the kerosenes have been removed leads to a series of distillates of gradually increasing viscosity, these constituting the lubricating oils. On chilling these distillates paraffin wax crystallises and may be pressed out and refined ; the m. pt. of the waxes depends largely on the cut of the vacuum oil from which they are prepared, and they comprise the paraffins C_{18} to C_{43},[1] together with other hydrocarbons. Apart from the so-called ' crystalline ' paraffin wax, there is an amorphous wax which, instead of crystallising from the chilled cut, causes it to solidify into a gel, which after filtration through bleaching earth gives the petroleum jelly or soft paraffin (' paraff. molle ') of the pharmaceutical chemist. However useful it may be in compounding ointments and cosmetics, its appearance is viewed with disfavour by refiners, as it monopolises a considerable proportion of the valuable lubricating oils and in normal times is usually in excess of demand. Practically nothing is known concerning the chemical individuals present in these higher fractions.

It may be added that there are other types of substances present in petroleum besides hydrocarbons ; oxygen compounds such as naphthenic acids and phenols are found, and the residue from removal of the vacuum oils contains a high proportion of oxygen-containing asphalts. Sulphur compounds are almost invariable constituents, and some crudes contain nitrogenous bodies ; some of these constituents are set out in the table below :—

TABLE XXXVI

Sulphur compounds			Nitrogen Compounds
		b.	
Hexylthiophan	$C_6H_{12}S$	55–57/50 mm.	β-Methylquinoline 2, 3, 8-Triphenylquinoline 5, 6-Dihydropyrindene (340)  (340)  (341) Derivatives of pyrindacine (341)
Heptylthiophan	$C_7H_{14}S$	74–76/50 mm.	
Octylthiophan	$C_8H_{14}S$	81–83/50 mm.	
iso-Octylthiophan	$C_8H_{14}S$	94–96/50 mm.	
Nonylthiophan	$C_9H_{18}S$	106–108/50 mm.	
Decylthiophan	$C_{10}H_{20}S$	114–116/50 mm.	
Undecylthiophan	$C_{11}H_{22}S$	128–130/50 mm.	
Tetradecylthiophan	$C_{14}H_{28}S$	168–170/50 mm.	
Hexadecylthiophan	$C_{16}H_{32}S$	184–186/50 mm.	
Octadecylthiophan	$C_{18}H_{36}S$	198–202/50 mm.	
Thiophen	C_4H_4S	80°	
Ethyl sulphide	$(C_2H_5)_2S$		
Propyl sulphide	$(C_3H_5)_2S$		
Butyl sulphide	$(C_4H_9)_2S$		
Ethyl thiol	C_2H_5SH		
iso-Propyl thiol	C_3H_7SH		
iso-Butyl thiol	C_4H_9SH		
Thiophthen			
Alkyl thiophthens			

Finally, it may be added that the ash from the petroleum coke left behind is often rich in vanadium and nickel. Thus, crudes from Kansas give an ash containing up to 20 per cent. of V_2O_5 and 6 per cent. of NiO. This vanadium is used industrially.

CRACKING AND REFORMING

The study of cracking and reforming in the petroleum industry has become almost a science in itself. Over half the gasoline used to-day is cracked spirit

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[1] Buchler and Graces, *Ind. Eng. Chem.*, 1927, **19**, 718.

—and it is no exaggeration to say that this alone has had a profound effect on engine design. Since petroleum fractions are of so complex a composition it is not to be expected that any very simple indication can be given of what takes place during cracking; but reference to the formulæ below will indicate something of the possibilities :—

$$\begin{array}{llcl}
\big| & CH_3[CH_2]_4CH_2CH.CH_2CH_2CH_3 & & \\
\big| & CH_3[CH_2]_4CH_2CH_2CH_2CH{=\!=}CH_2 & + & H_2 \\
\big| & CH_3[CH_2]_4CH_2CH_2CH_2CH_3 & + & \text{ethylene } (\textit{via } 2CH_2 \rightarrow C_2H_4) \\
\big| & CH_3[CH_2]_4CH_2CH_2CH{=\!=}CH_2 & + & CH_4 \\
\big| & CH_3[CH_2]_1CH_2CH_2CH_3 & + & CH_2{=\!=}CH_2 \\
\big| & CH_3[CH_2]_4CH_2CH{=\!=}CH_2 & + & CH_3 \,.\, CH_3 \\
\big| & CH_3[CH_2]_4CH_2CH_3 & + & CH_2{=\!=}CH \,.\, CH_3 \\
\downarrow & CH_3[CH_2]_4CH{=\!=}CH_2 & + & CH_3 \,.\, CH_2 \,.\, CH_3
\end{array}$$

These changes are ‘ idealised ’ in the sense that they represent the gradual removal of fragments of gradually increasing size from the original decane structure. It takes no account of the following facts :—

(1) That during pyrolysis coke and hydrogen are often produced.
(2) Dienes are obtained by double degradation of the stem.
(3) That several of the smaller fragments can recombine to form branched chain hydrocarbons.
(4) That cyclisation may be induced with the formation of naphthenes and aromatics.

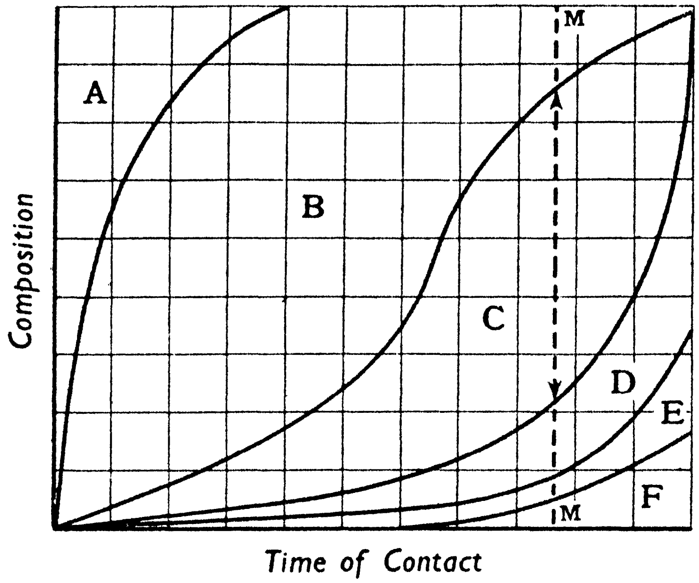
Thus, cracking may produce almost any type of hydrocarbon mixture. Thermodynamic considerations of the free energies of the various hydrocarbons will enable the refiner to tell whether a given reaction is feasible, but only experience can tell him the necessary time factor. Thus, in a given decomposition a hydrocarbon, H_A, may decompose in two different ways to give :—

$$\begin{array}{ll}
\text{(i)} & H_A \longrightarrow H_B + H_C. \\
\text{(ii)} & H_A \longrightarrow H_D + H_E.
\end{array}$$

Thermodynamically the free energies concerned may indicate that reaction (i) is more likely to preponderate over (ii); but if the reaction rate of (ii) is more rapid than that of (i), then this condition will be reversed. The time, pressure and temperature of contact and the composition of the cracking stock are all factors of paramount importance in the nature of the cracked spirit. The diagram below gives some indication of the effect of time of contact on the nature of the product.

It should be added here that the type of petrol or gasoline obtained by this process of cracking is much more suitable for use in the modern high compression internal combustion engine than is the straight-run gasoline from the original oil. Thus the compression ratio suitable for an engine on straight-run petrol is 1 : 3 ; that for one on good cracked spirit is 1 : 7, or even 1 : 8. Thus, straight-run petrol is of little industrial value, and is usually itself cracked or ‘ reformed ’ by cracking under pressure to obtain a mixture of more unsaturated and arborescent hydrocarbons which are more suited to the modern engine. This process is often known as ‘ up-grading ’.

It must also be emphasised that during the process of cracking vast quantities of simple gaseous unsaturated hydrocarbons are obtained—ethylene, propylene, butene and pentenes which are amongst the most important raw materials for organic synthesis (Fig. III) (see also p. 81).



A. Unchanged cracking stock.
B. High boiling, partly cracked stock, over gasoline range.
C. Gasoline.
D. Gas.
E. Tar.
F. Coke.

FIG. III.

It is clear that the optimum time is that represented by the vertical line MM.[1]

APPENDIX III

RUBBER AND ITS ANALOGUES

Natural rubber examined from a chemical point of view, appeared to be a complex hydrocarbon, and was accorded a formula $(C_5H_8)_n$. Several observers [2] had noted a volatile hydrocarbon C_5H_8 formed by the distillation of rubber, but it remained for Tilden [3] in 1882 to determine the structure of isoprene, the structural unit of rubber. Examination of isoprene followed, and it was soon realised that isoprene could be converted into rubber-like polymers ; in fact, Tilden in 1884 [4] remarked

> " . . . if it were possible to obtain this hydrocarbon (isoprene) from some other and more accessible source the synthetical production of India rubber could be accomplished."

from which it is clear that he realised the industrial significance of this work.

There has been much acrimonious dispute as to who really discovered ' synthetic rubber ', much depending on the practical definitions accorded to ' synthetic ' and ' rubber '. The facts appear to be as follows :—

1860 Williams,[5] obtaining isoprene from rubber, allowed it to stand for some months, and noticed an increase in viscosity ; on distillation of this viscous syrup there remained behind a " pure white spongy elastic mass " which had the properties of rubber, but which contained 10·5 per cent. of oxygen, corresponding to one atom of the latter to each pair of isoprene units.

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[1] Scholl *et al.*, *Ber.*, 1910, **43**, 2202.

[2] Himly, *Ann.*, 1838, **27**, 40 ; Williams, *Proc. Roy. Soc.*, 1860, **10**, 516 ; Bouchardat, *Bull. Soc. Chim.*, 1875, **24**, 108.

[3] Tilden, *Chem. News*, 1882, **46**, 120.

[4] Tilden, *J.C.S.*, 1884, **47**, 411.

[5] Williams, *Phil. Trans.*, 1860, **150**, 245.

1879 Bouchardat[1] having distilled rubber, and obtained a crude isoprene, found that it could be converted by dilute aqueous hydrochloric acid into a material resembling rubber, but which contained a small amount of chlorine (1·7 per cent.) which Bourchardat himself regarded as contamination, but which may probably be due to the addition of hydrogen chloride to a small proportion of the double bonds of the polymer. Ignoring this small amount of chlorine, Bourchardat's polymer had the formula $(C_5H_8)_n$. His comment, after detailing the physical properties of the material was " . . . all these properties appear to identify this polymer of isoprene with the substance from which isoprene is formed, namely rubber."

1882 Tilden, *loc. cit.* Produced isoprene by an alternative route—the pyrolysis of turpentine.

1892 Tilden [2] reported that after standing for some time in a sealed bottle isoprene from turpentine had changed, and that in the syrup were "several large masses of solid, of a yellowish colour. Upon examination this turned out to be indiarubber ".

If by 'synthesis' is meant the production of the final product by a process involving an alternative method of producing the intermediate (i.e., in this case an alternative method of making isoprene) then no true synthesis could be carried out until after Tilden's work in 1882. If by 'rubber' is meant a product identical in all chemical and mechanical respects with natural rubber, in which the 'n' of $(C_5H_8)_n$ is equal to that in true natural rubber, then, as far as we are aware, no true 'synthetic rubber' has ever been made. What Williams, Bouchardat and Tilden achieved was the 'proximate synthesis', and their products were 'artificial rubbers', similar to but not identical with the natural material. This does not, however, detract from the value of their work, and it appears that Tilden's product must have approximated most closely to a true synthetic rubber.

During the period 1900–1910 much attention was focussed on the structure of rubber and the possibilities of its industrial synthesis, the critical operation being the initiation of the polymerisation of isoprene. Harries, in conjunction with the Bäyer Co., and the Badische Anilin und Soda Fabrik, had carried out extensive work on the structure of rubber, and had discovered the influence of metallic sodium on the polymerisation of isoprene, about the same time as Matthews and Strange, a British syndicate. The latter filed their Patent on October 25th, 1910; [3] Harries and his firm on December 12, 1910. Thus, the British investigators held priority, and maintained it in face of legal opposition. The German investigators made the matter of priority of *discovery* (apart from priority of Patent) a subject for bitter controversy, in which accusations and claims were made which were undignified, to say the least; readers who are interested in the course of the quarrel should consult Harries [4] and Scholtz,[5] and also Barron's account in his recent book.[6]

From 1910 onwards through the war of 1914–1918 work on artificial rubber received impetus from two sources—the price of natural rubber rose to as high as 15s. lb.; during 1914–1918 the combatant nations, more especially Germany, experienced a shortage of rubber. Both factors led to a concentration of effort towards synthesis of rubber-like materials, but although the materials were successful enough as 'stop-gaps', their manufacture ceased with the war and the advent of cheap rubber from the plantations. Since 1920 the viewpoint has changed; now instead of adhering tenaciously to the principle of essaying the production of a commodity exactly the same as rubber chemically and mechanically, it has been realised that it is largely the mechanical properties of natural rubber that are desirable, and that the nature of the molecule matters little as long as these mechanical properties are maintained ; indeed, with some of the newer artificial materials the chemical and physical resistance of rubber is surpassed.

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[1] Bouchardat, *C.R.*, 1879, **89**, 117.

[2] Tilden, 1892. In a paper to the Birmingham Philosophical Society.

[3] Matthews and Strange, B.P. 24,790/1910.

[4] Harries, *Ann.*, 1912, **395**, 211.

[5] Scholtz, "Synthetic Rubber", Benn, London, 1926.

[6] Barron, "Modern Synthetic Rubbers", London, 1942.

THE CLASSIFICATION OF ELASTIC MATERIALS

The writer has, so far, avoided the use of the term 'synthetic rubber' which should logically be reserved for an artificially produced material identical in all respects with natural rubber. Such a substance has not yet been produced, although many substances are in bulk production which have some, if not all, the properties of natural rubber ; many such substances are like rubber itself, hydrocarbons, but others are based on chlorinated hydrocarbons, or sulphur compounds. The classification of elastic materials given in the table opposite is based on that suggested by Barron (*loc. cit.*), and is simple and easily remembered. The classification avoids the use of 'elastoplast', which unfortunately, happens to be a registered trade-name, and introduces only one new term 'synthelast', a portmanteau word indicating the field of synthetic elastic materials.

The table also indicates the main sources of the monomers from which the various types of synthelasts may be obtained, from which it will be noted that the bulk of these materials are derived from petroleum or acetylene—a small contribution being made from the hydrocarbons of coke oven gas.

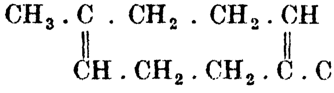
NATURAL RUBBER STRUCTURE

There is little doubt that rubber may be regarded as an unsaturated hydrocarbon of the empirical formula $(C_5H_8)_n$; it is soluble in various organic solvents, e.g., benzene, carbon disulphide, dipentene, etc., and shows its unsaturation by combining with oxygen, halogens and nitrosyl chloride. The combination of rubber with sulphur (the process of vulcanisation) enables it to retain its elastic properties at the same time as its resistance to wear is considerably increased.

Harries [1] expended much ingenuity on attempts to elucidate the structure of natural rubber, and developed the method of ozonolysis as a guide to the structure of unsaturated hydrocarbons. He obtained levulic aldehyde (with some levulic acid) by hydrolysing rubber ozonide and unfortunately concluded

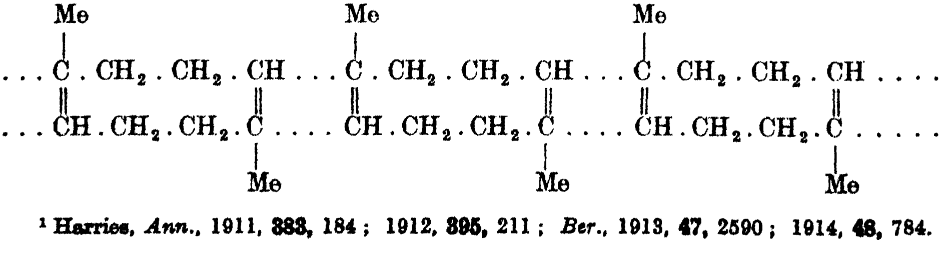
$$CH_3 . CO . CH_2 . CH_2CHO \qquad CH_3 . CO . CH_2CH_2COOH$$

that the structure of rubber involved an eight-membered ring, and was derived from dimethyl *cyclo*öctadiene :—



$$\begin{array}{l} CH_3 . \overset{}{C} \;.\; CH_2 \;.\; CH_2 . CH \\ \qquad \| \qquad\qquad\qquad\quad \| \\ \qquad CH . CH_2 . CH_2 . C . CH_3 \end{array}$$

presumably by a polymerisation through the partial valencies. Harries therefore regarded rubber as embodying the structure :—



$$\begin{array}{l} \mathrm{Me} \qquad\qquad\qquad\qquad\qquad \mathrm{Me} \qquad\qquad\qquad\qquad\qquad \mathrm{Me} \\ \ldots C . CH_2 . CH_2 . CH \ldots C . CH_2 . CH_2 . CH \ldots C . CH_2 . CH_2 . CH \ldots . \\ \ldots CH . CH_2 . CH_2 . C \ldots . CH . CH_2 . CH_2 . C \ldots . CH . CH_2 . CH_2 . C \ldots . . \\ \qquad\qquad\qquad \mathrm{Me} \qquad\qquad\qquad\qquad\qquad \mathrm{Me} \qquad\qquad\qquad\qquad\qquad \mathrm{Me} \end{array}$$

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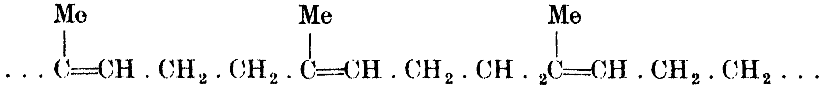
[1] **Harries**, *Ann.*, 1911, **383**, 184 ; 1912, **395**, 211 ; *Ber.*, 1913, **47**, 2590 ; 1914, **48**, 784.

He claimed at one time to have isolated a *cyclo*öctadione derivative but later admitted he was in error on this point. Harries suffered from the 'ideé fixe' and refused to accept the overwhelming evidence which was gradually forthcoming in favour of the linear polymer structure for rubber as put forward by Pickles,[1]



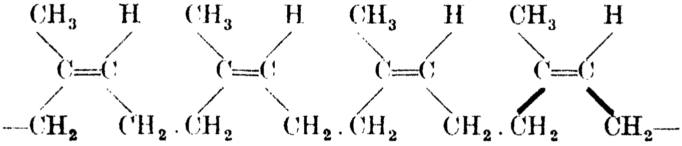
$$\ldots \overset{\text{Me}}{\text{C}}{=}\text{CH} \,.\, \text{CH}_2 \,.\, \text{CH}_2 \,.\, \overset{\text{Me}}{\text{C}}{=}\text{CH} \,.\, \text{CH}_2 \,.\, \text{CH} \,.\, {}_2\overset{\text{Me}}{\text{C}}{=}\text{CH} \,.\, \text{CH}_2 \,.\, \text{CH}_2 \ldots$$

which is the accepted basis for the modern conception of rubber. It will be noted that levulic aldehyde would be a predominant product of ozonolysis of such a structure.

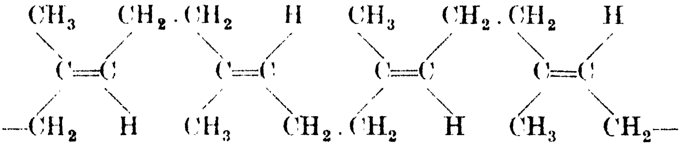
The three important problems which the Pickles formula does not explain or deal with are :—

(1) The stereochemical structure of the chain.
(2) The length of the chain, i.e., the value of n, in $(C_5H_8)_n$.
(3) The relation of elastic properties to the structure.

Regarding the first of these, it is clear that the sequence of unsaturated links in Pickles' formula is capable of *cis*- and *trans*-isomerism. Staudinger has used this to account for the differences between rubber and guttapercha, which he regards as *cis*- and *trans*-isomers.



Trans- form ; natural rubber



Cis- form ; Guttapercha

Guttapercha, which is empirically a rubber-isomer, is deficient in the elasticity characteristic of rubber, but both guttapercha and rubber yield the same *cyclo*rubber on treatment with cyclising agents.[2]

The question of molecular weight of rubber does not appear to be capable of solution ; indeed, the older conception of linear polymers as built up of molecules with a definite number of units, is giving way to the view that the term " molecule " ought not to be used in connexion with such substances, and that the solid materials do not necessarily involve a repetitive molecular structure. This has been considered at some length by Staudinger, who regarded linear polymers of this class as belonging to the group of 'giant molecules' of infinite size. Attempts made to determine the molecular weight of rubber by depression of the freezing point of solvents have given a variety of values ranging from 10,000–250,000, or from 200–4400 isoprene units.[3]

The elastic properties of linear polymers have never been satisfactorily explained, and older theories built up on the unsaturation of natural rubbers and early syntholasts have been discarded in the light of modern work on linear polymers such as polyisobutene, which are fully saturated and which, nevertheless, still have the mechanical properties of rubber. It is, of course, true that the chemical properties of natural rubber are bound up with its unsaturated character; thus, its great drawback—'ageing' due to oxidation—its reactivity with halogens, its capacity for vulcanisation with sulphur are all manifestations of its unsaturation, and as such are absent from the saturated linear polymers. Thus, the conception of rubber as a linear polymer is satisfactory from a chemical standpoint, but sheds no light on the mechanical properties. It is fairly certain that in a mass of rubber the linear molecules are not orientated in bundles (fibro-structure) but approach (at any rate in the raw, unworked state), a random distribution. There is also evidence that during the process of stretching some, if not all, of those linear polymers parallel to the applied force are literally pulled into fragments; recovery involves the rejoining of a large proportion of the fragments; fatigue is that point where the proportion of fragments which do not rejoin becomes appreciable, and complete elastic return is not possible.

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[1] Pickles, *J.C.S.*, 1910, **97**, 1085.
[2] Ferri, *Chim. Helv. Acta*, 1938, **20**, 149.
[3] Schade, *Rubber Age* (*N.Y.*), 1941, **48**, 387.

SYNTHELASTS

A large variety of simple unsaturated molecules form linear polymers involving the repetition of a single unit. Examples are shown in the table below:—

TABLE XXXVIII

Components	Linear polymer. Unit shown in brackets	Name
Butadiene	$-CH{=}CH \cdot CH_2[CH_2 \cdot CH{=}CH \cdot CH_2]-CH_2CH{=}CH-$	S.K.B. Rubber Buna (85–115)
Butadiene + styrene	$-CH_2 \cdot CH\phi \cdot CH_2[CH_2 \cdot CH{=}CH \cdot CH_2 \cdot CH\phi \cdot CH_2]-CH_2 \cdot CH{=}CH-$	Buna S and SS
Butadiene + acrylic nitrile	$-CH_2-CH(CN)CH_2[CH_2 \cdot CH{=}CH \cdot CH_2CH(CN)CH_2]-CH_2 \cdot CH{=}CH-$	Buna N, Hycar Chemigum Perbunan
Butadiene + isobutene	$-CH_2C(CH_3)_2CH_2[CH_2 \cdot CH{=}CH \cdot CH_2C(CH_3)_2CH_2]CH_2 \cdot CH{=}CH-$	Butyl Rubber
Chlorobutadiene	$-CCl{=}CH \cdot CH_2[CH_2 \cdot C(Cl){=}CH \cdot CH_2]CH_2 \cdot CCl{=}CH-$	Neoprene
Isobutene	$-C(CH_3)_2CH_2[C(CH_3)_2 \cdot CH_2]C(CH_3)_2-$	Vistanex
Vinyl chloride	$-CH_2 \cdot CHCl[CH_2 \cdot CHCl]-CH_2-$	Vinylite Q Koroseal Flamenol
Dichloroethylether + disodium tetra-sulphide $(ClCH_2 \cdot CH_2)_2O + Na_2S_4$	$CH_2CH_2-S_4-[CH_2CH_2OCH_2CH_2\underset{\substack{\downarrow \\ S}}{S}-\underset{\substack{\downarrow \\ S}}{S}-]CH_2CH_2-$	Thiokol B

The raw materials for these substances are shown in Table XXXVII, and it will have been noted that with one or two minor exceptions they are derived from the petroleum or carbide sections of industry. The industrial production of synthelasts is divisible into two main parts; the production of the raw materials and the inducing of polymerisation. The problems relating to the first part are dealt with elsewhere in this work; it is, however, necessary to say something here about the problems of polymerisation as they affect synthelasts.

When chemical entities such as butadiene, C_4H_6, polymerise, the commonly accepted conception as put forward by Staudinger is that of the formation of a macro-molecule—a straight uninterrupted chain of monomeric units. The properties of the polymers depend on the length of the chain; with dimers and simple polymers, rise in boiling point and increase in viscosity are the most obvious features; as the length of the chain increases so the viscosity increases until at a certain point the polymers cease to have the outward characteristics of viscous liquids, and take on many highly desirable mechanical attributes.

Thus, synthelasts show the elasticity of rubber, but acrylic ester becomes a soft 'glass' of resilience and strength, and methyl methylacrylate gives high polymers which are tough, elastic and transparent with a very high transmissibility for light. Thus, whilst some chains develop rubber-like mechanical properties, others show a transparent 'plastic' structure. This indicates that the problems of synthetic rubber and of 'plastics' are similar, if not identical.

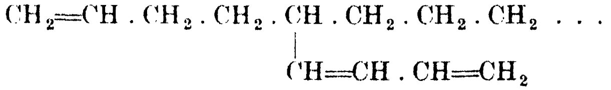
The linear polymer theory of Staudinger has been extended by Mark and Rath [1] to cover two and three dimensional polymers. Simple probability considerations would indicate that the formation of unbranched linear polymers is an idealisation, or a simplification of what actually happens. In general, the factors leading to two or three dimensional polymers are :—

(1) Branching.
(2) Cross linkages.
(3) Cyclisation.

Thus, with butadiene the ideal conception of a linear polymer involves :—

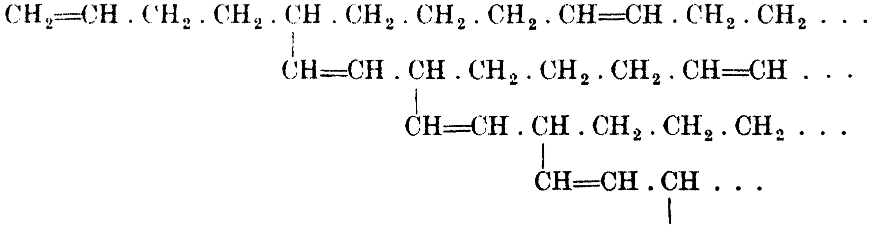
$$CH_2{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2\,.\,CH_2\;.\;.\;.$$

but if a further molecule of butadiene were to react thus :—



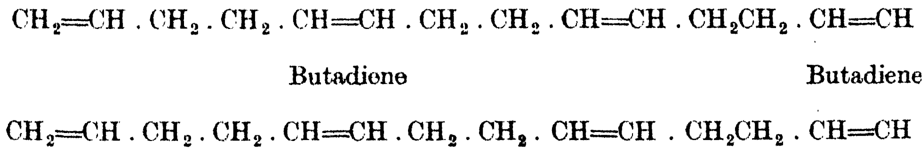
$$CH_2{=}CH\,.\,CH_2\,.\,CH_2\,.\,\underset{\overset{|}{CH{=}CH\,.\,CH{=}CH_2}}{CH}\,.\,CH_2\,.\,CH_2\,.\,CH_2\;.\;.\;.$$

the chain will become arborescent, and by continuation of the process a nominal two dimensional structure may be arrived at :—



The mechanical properties of synthelasts depend largely on the extent to which arborescence, in preference to linear polymerisation, takes place.

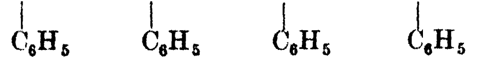
The existence of cross linkages also affects the properties tending to increase brittleness at the expense of elasticity. The diagram below shows the type of structure characterised by the term 'cross linkage', and is in respect of the butadiene polymer.



$$CH_2{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2CH_2\,.\,CH{=}CH$$

$$CH_2{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2CH_2\,.\,CH{=}CH$$

A particularly good example of non-linear polymerisation is the effect of low percentages (1–2 per cent.) of divinylbenzene on polystyrene formation. In the absence of impurities polystyrene :—



$$-\underset{C_6H_5}{\underset{|}{CH}}\,.\,CH_2\,.\,\underset{C_6H_5}{\underset{|}{CH}}\,.\,CH_2\,.\,\underset{C_6H_5}{\underset{|}{CH}}\,.\,CH_2\,.\,\underset{C_6H_5}{\underset{|}{CH}}\;.\;.\;.$$

is formed from styrene. The addition of a few per cent. of divinylbenzene leads to an entirely different polymer, insoluble in solvents which easily take up polystyrene. In this case, the presence of an occasional disubstituted benzene polymer links up the linear polystyrene chains to form a two or three dimensional lattice :—

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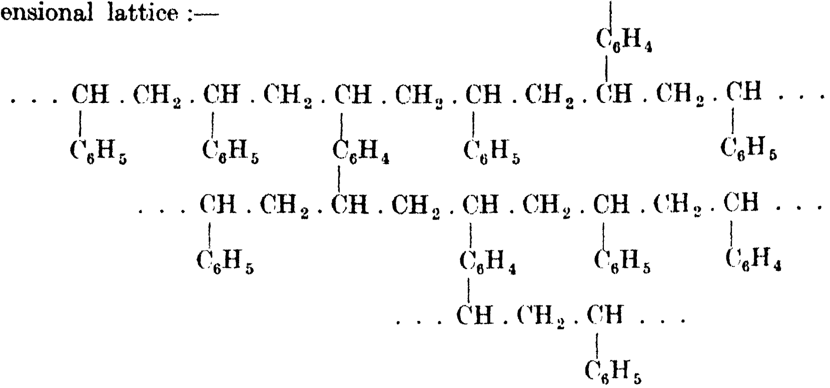
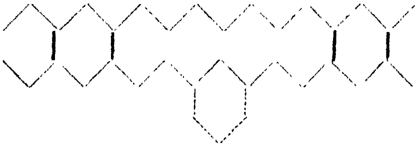
[1] Mark and Rath, "High Polymeric Reactions" (N. York), 1941.



$$\begin{array}{ccccccccccccc}
 & & & & & & & & & \mathrm{C_6H_4} & & & \\
 & & & & & & & & & | & & & \\
\ldots & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & \ldots \\
 & | & & | & & | & & | & & & & | & \\
 & \mathrm{C_6H_5} & & \mathrm{C_6H_5} & & \mathrm{C_6H_4} & & \mathrm{C_6H_5} & & & & \mathrm{C_6H_5} & \\
 & & & & & | & & & & & & & \\
 & & \ldots & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & \ldots \\
 & & & | & & & & | & & | & & | & \\
 & & & \mathrm{C_6H_5} & & & & \mathrm{C_6H_4} & & \mathrm{C_6H_5} & & \mathrm{C_6H_4} & \\
 & & & & & & & | & & & & & \\
 & & & & & & \ldots & \mathrm{CH} & .\mathrm{CH_2}. & \mathrm{CH} & \ldots & & \\
 & & & & & & & & & | & & & \\
 & & & & & & & & & \mathrm{C_6H_5} & & &
\end{array}$$

Cyclisation is another process which leads to modification of the properties of a synthelast ; the elasticity is frequently diminished but not to the extent of brittleness, and difficulties due to steric factors are met with when such polymers are submitted to vulcanisation. Cyclisation can be of various types ; the commonest met with is the formation of a ring at intervals in the chain, a process which is more easily understood if the formal straight-chain notation of these hydrocarbons is abandoned. If the chain is written thus :—



(342)

the cyclisation may be conceived as the completion of a ring, or rings, by subsidiary links, or protrotopic action, as indicated by the thick lines above. Cyclisation can also take the form of an added ring, as indicated in the dotted lines in (342), where the rings appear as excrescences on the linear polymeric chain. The progress of a reaction such as the polymerisation of a difunctional monomer (e.g., butadiene) almost inevitably produces a mixture of medium length polymers and of macro-molecules (both the latter being considered as linear), together with a varying proportion of two-dimensional structures. The mechanical properties of the finished synthelast will depend on the varying proportions of these constituents, and this in turn on the course of the polymerisation. It is clear, therefore, that the manner in which the polymerisation is brought about is of fundamental importance. The various conditions under which polymerisation is effected are :—

(1) Direct polymerisation in the gaseous phase.
(2) Direct polymerisation in the liquid phase.
(3) Polymerisation in solution.
(4) Polymerisation of a dispersion.

Gaseous polymerisation has received practical application in this field, by the conversion of ethylene to polythene, but the earliest attempts to obtain synthelasts were by liquid phase polymerisation of diolefines such as butadiene and isoprene, more particularly the latter. The results, although encouraging, were not suited to large-scale work, and had the overwhelming disadvantage that successive runs, under apparently identical conditions, gave widely differing products. This now appears to be due to catalytic influences of small traces of impurities. The use of ' directive ' catalysts (i.e., small traces of substances capable of directing the polymerisation almost exclusively towards one particular end-product) was initiated by the use of metallic sodium, first discovered in this capacity during attempts to purify isoprene by distillation over metallic sodium. At first the sodium was used in wire form, but later, dispersions of the metal in dry paraffin were used, and a more modern development is the use of surfaces of sodium deposited on combs or rods of zinc.[1] Even with the improvements effected by the use of metallic sodium, control of liquid phase polymerisation is difficult, and the best results of sodium polymerisation are attained when the diolefine is diluted with an inert solvent such as benzene or *cyclo*hexane, or when substances such as dioxane and amines such as aniline are added. The use of high pressures has also been investigated, and has resulted in processes for the direct polymerisation of simple olefines, e.g., ethylene to ' Polythene ', a substance having some of the properties of a synthelast.

Since the polymerisations described in the previous paragraph are exothermic, they are difficult to control, and even under the best conditions the difficulty arising from differences of properties in successive and apparently identical batches is only diminished, and not entirely removed. By dispersing the monomer in an inert aqueous phase and carrying out the polymerisation in the emulsion, many of the difficulties of homogeneous phase polymerisation disappear. The heat of reaction is rapidly dispersed and the ' grain ' of the emulsion controls the properties of the final polymer. The process is in wide and increasing use, especially for the Thiokol types.

Emulsion polymerisation has proved of the greatest value in the large-scale production of synthelasts, as it enables large batches to be controlled and a tolerably uniform product to be produced. To dispel any illusions as to the simplicity of this process, the following summary of the comments of Mark and Rath (*loc. cit.*) on the subject are given. Up to ten components are needed to build up a colloid system for emulsion polymerisation :—

1. *The basic phase.*	Demineralised water free from organic impurities (60–80 per cent.).
2. *The main monomer.*	Butadiene, vinyl chloride, etc., present in proportion of 15–30 per cent.
3. *The additional monomers.*	Styrene, acrylic nitrile ; 5–15 per cent. of the emulsion.
4. *The emulsifier.*	To produce the colloid dispersion ; often a sulphonated fatty alcohol or acid.
5. *The stabiliser.*	An additional colloid to prevent premature discharge of the emulsion ; casein, glue, starch and gums are common in this capacity.
6. *Surface tension regulator.*	Present to maintain the most favourable emulsion particle size. Aliphatic alcohols C_5—C_8 are most commonly used.
7. *The catalyst.*	The main function of which is to accelerate the formation of polymer. Ozone, hydrogen peroxide, organic peroxides and peroxide salts are commonly used.
8. *The regulator.*	The mechanism by which regulators act is uncertain, their effect is to cut down branching and to limit polymerisation, as far as possible, to linear forms. Chlorinated aliphatic hydrocarbons are successful in this function.

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[1] Nebidozsky, *Bull. Ass. Chim.*, 1938, **55**, 215.

9. *pH controller.* Since the particle size is a critical factor, and is susceptible to pH alterations, a buffer salt, usually an acetate or phosphate, is added to the mixture.

It now remains to add something about co-polymerisation, the process of polymerising two monomers at once. This is a technique borrowed from the plastics industry where the most notable instance is the co-polymerisation of vinyl acetate and vinyl chloride. If these substances are polymerised individually, materials are obtained of little practical interest; that from vinyl acetate is soft, too thermophastic for use, absorbs water, is chemically non-resistant; that from vinyl chloride is only slightly thermoplastic, and although somewhat brittle, is chemically resistant to a high degree. No method of mixing of the two polymers proved satisfactory in blending their qualities, and co-polymerisation of the monomers was resorted to; the product retained the chemical and wetting resistance of the chloride polymer, but also acquired the thermoplasticity and solubility of the polymeric acetate.

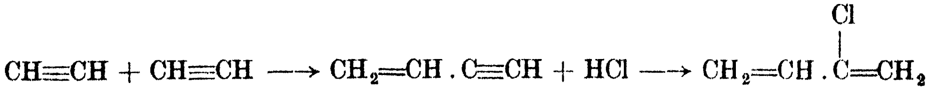
Applied to synthelasts, the co-polymerisation of butadiene with styrene, vinyl chloride or acrylic nitrile yields materials superior in many respects to those obtained by the polymerisation of butadiene alone, and a considerable proportion of industrial 'synthetic rubber' is co-polymerised material.

INDUSTRIAL SYNTHELAST MATERIALS

The highest tonnage of industrial synthelasts is undoubtedly of butadiene co-polymerised with resin intermediates. German firms produced sodium-polymerised butadiene or 'buna' (*BU*tadiene -*NA*trium) rubbers which were characterised by numbers, e.g., buna-85, buna-115, and this manufacture was taken up by Russia for their 'S.K.A.' and 'S.K.B.' which are still produced in very considerable quantity (60,000 tons in 1939). The Germans, however, largely dropped the straight-run butadiene polymers in favour of co-polymerised materials, thus initiating the Perbunan series (Perbunan and Perbunan-Extra and Buna-S). All the latter, together with Hycar and Chemigum, are produced in the United States in considerable and increasing quantity.

Buna-S is a co-polymer of butadiene with styrene, and although it offers no advantage over natural rubber in respect of solvent and oil resistance, it is superior in abrasion resistance. This fact is of great importance to the tyre industry, which absorbs a considerable percentage of the rubber output of the world, and the United States has adopted Buna-S as a standard material for large scale tyre production.

Neoprene is another synthelast of outstanding properties and importance; when Nieuwland, in 1925, prepared vinylacetylene by passing acetylene into aqueous cuprous chloride, the foundation was laid for the production of neoprene. The vinyl acetylene is produced in good yield and gives with hydrochloric acid the monomer



$$CH\equiv CH + CH\equiv CH \longrightarrow CH_2{=}CH\,.\,C\equiv CH + HCl \longrightarrow CH_2{=}CH\,.\,\overset{\overset{Cl}{|}}{C}{=}CH_2$$

2-chlorobutadiene-1, 3 (chloroprene). Linear polymers of varying length can be produced by polymerising chloroprene, either *en masse* or in emulsion form, which are characterised by marked resistance to oil and solvents. Neoprene was not introduced as a 'substitute' rubber, but as a product specifically devised to meet needs with which natural rubber was unable to cope; such as hoses and valve diaphragms for ether, petrol and similar solvents, for vegetable and lubricating oils. The present annual tonnage of Neoprene approaches

100,000 and its superiority to natural rubber for special purposes has been demonstrated by twelve years of industrial use.

In general, it may be remarked that the industrial development of synthelasts has been a story of persistence over half a century ; Tilden's vision in 1884 of 'a synthetical India rubber' has many times during the last sixty years been described as 'uneconomic' or 'impractical' but has, nevertheless, been pursued to a satisfactory conclusion.

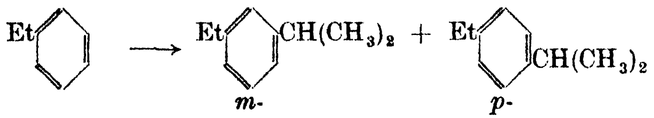
APPENDIX IV

THE FRIEDEL AND CRAFTS REACTION

In the spring of 1877 C. Friedel and J. M. Crafts, two workers in the laboratories of Würtz in Paris, published a paper[1] on a new reaction in which anhydrous aluminium chloride was used as a reagent for inducing the elimination of hydrogen chloride from hydrocarbons and organic halogen compounds. They realised the importance of the reaction as a new method of preparing alkyl derivatives of aromatic hydrocarbons, and in a remarkably short space of time extended their new reaction to the preparation of di- and tri-aryl methanes, ketones using phosgene and acyl chlorides, and a variety of other compounds. Between the years 1877 and 1888 these two workers laid the foundations of a section of organic chemistry which has proved invaluable in all fields of investigation.[2] Two summaries[3] were published of their work by the authors themselves, and Friedel died one year after the publication of the second.

Thus, in their joint investigations, Friedel and Crafts had given to chemical science methods of preparing hydrocarbons, ketones, di- and tri-aryl methanes, aurins, anthracene derivatives, anthraquinone, thiophenol, diphenylene sulphide and many others ; they had discovered the disproportionating action of aluminium chloride on aliphatic hydrocarbons, and had patented the use of anhydrous aluminium chloride for the refining of petroleum products. Others have since added to and extended the range of these reactions, but valuable as these additions have been, it has to be conceded that few, if any, were not covered by the work of the two originals.

Examples of the use of the Friedel-Crafts reaction for building up substituted aromatic hydrocarbons are innumerable, and almost every conceivable polyalkyl benzene has been prepared in this way. It appears to be a general rule that second and third alkyl groups entering an aromatic ring under the influence of aluminium chloride, take up positions *m*- or *p*- to the existing substituent, e.g., ethylbenzene and *iso*propyl chloride give a mixture of *m*- and *p*-ethyl*iso*propylbenzene (343) with very little *ortho*-isomer ; when *m*-xylene is treated with



(343)

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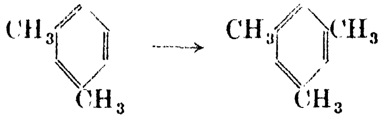
[1] Friedel and Crafts, *Bull. Soc. Chim.*, 1877, 2, **27**, 530.

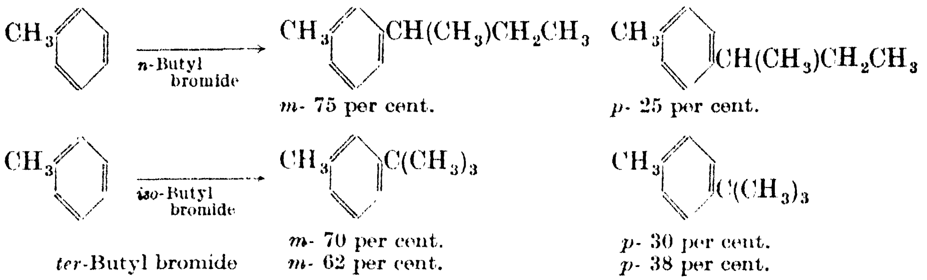
[2] Friedel and Crafts, *C.R.*, 1877, **84**, 1392, aromatic alkyl derivatives ; 1877, **85**, 74, use of ferric chloride ; 1877, **84**, 1450 CCl_4 and $CHCl_3$; 1878, **86**, 884, sulphur ; 1878, **86**, 1368, CO_2, SO_2 1880, **91**, 257, Tetra, penta, hexamethylbenzene ; 1881, **92**, 833, Phthalic anhydride ; 1885, **100**, 792, theoretical ; 1885, **101**, 1218, separation of xylenes and ethylbenzene ; Friedel and Crafts, *Bull. Soc. Chim.*, 1877, 2, **28**, 50 $CHCl_3$ and CCl_4 : 1878, 2, **29**, 49, Phthaloyl chloride ; 1878, 2, **29**, oxidation w $AlCl_3$; 1878, 2, **30**, 146, other halides ; 1878, 2, **30**, 531, aniline ; 1882, 2, **37**, 49, petroleum hydrocarbons ; 1882, 2, **37**, 6, procedure ; 1884, 2, **41**, 322, methylene chloride ; 1885, 2, **43**, 53, autocondensation ; *Ann. Chim. Phys.*, 1887, 6, **11**, 263 ; Friedel and Crafts and Ador, *Ber.*, 1877, **10**, 1854 ; Friedel and Vincent, *Bull. Soc. Chim.*, 1881, **36**, 1 ; Friedel and Balsohn, *Bull. Soc. Chim.*, 1881, 2, **35**, 52.

[3] Friedel and Crafts, *Ann. Chim. Phys.*, 1884, 6, **1**, 449 ; 1888, 6, **14**, 433.



(344)

methyl chloride, mesitylene is almost the sole primary product (344). If a normal or secondary alkyl halide be used as an alkylating agent, rearrangement will take place if possible to a secondary or tertiary form. Thus, when toluene is alkylated the following results are obtained: in each case the *meta*-substituent

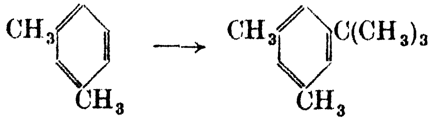


predominates, and a rearrangement of the alkyl group has taken place. Considerable work has been done to determine whether the entering alkyl group enters the *m*-position first, and then rearranges to the *para*-position, or whether the opposite course is followed. The suggestion that *para*-derivatives are first formed[1] has in general been upheld, and Norris and Rubinstein[2] have shown that at low temperatures *m*-xylene yields largely *p*-butyl derivative, but that the proportion of *m*-isomer rises with the temperature; Nightingale and Smith[3] have shown that *p*-butyl-*m*-xylene rearranges to the 1, 3, 5-isomer in the presence of aluminium chloride.

In general it has been noted that the more alkyl groups there are in the initial hydrocarbon, the easier it is to bring about the entry of a further group by the Friedel-Crafts reaction. Thus, 1, 3, 5-trimethylbenzene is almost quantitatively converted to 1, 2, 3, 5-tetramethylbenzene in a short space of time, whereas the conversion of benzene to toluene proceeds much more slowly.[4]

In the absence of an alkyl halide the alkylbenzenes react quite readily with aluminium chloride, dealkylation and rearrangement frequently take place; thus mesitylene gives not only some 1, 2, 3, 5-tetramethylbenzene but toluene and xylenes. Sometimes isomers unobtainable in other ways can be obtained by this method; 1, 2, 3-trimethylbenzene (hemimellitene) is not obtained by the action of methyl bromide on xylene in the presence of aluminium chloride, but is readily obtained by reacting xylene with aluminium chloride alone.[5]

One industrial application of this reaction in perfumery chemistry is the production of *ter*-butyl-*m*-xylene (346) for the preparation of musk xylene.



(345) (346)

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[1] Moyle and Smith, *J. Org. Chem.*, 1937, **2**, 112.
Schorger, *J.A.C.S.*, 1917, **39**, 2671.

[2] Norris and Rubinstein, *ibid.*, 1939, **61**, 1163.

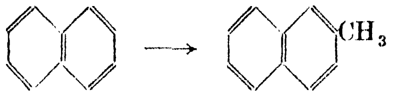
[3] Nightingale and Smith, *ibid.*, 1939, **61**, 101.

[4] Jacobsen, *Ber.*, 1881, **14**, 2624.

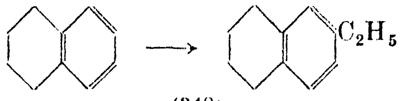
[5] Smith and Cass, *J.A.C.S.*, 1932, **54**, 1603.

m-Xylene (345) is the starting point; an ordinary Friedel-Crafts reaction with ter-butylchloride gives only a poor yield of the final hydrocarbon. By working below 50° and using only 2 per cent. of aluminium chloride the yield can be raised to above 90 per cent.[1] The same result is achieved [2] by using only a small proportion of *iso*butyl chloride and completing the reaction with gaseous *iso*butylene.

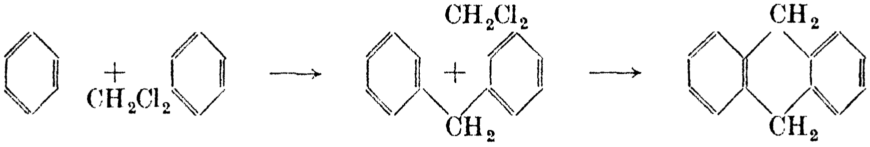
The extension of the Friedel-Crafts reaction to the naphthalene field has proved difficult, since all but the most mild conditions decomposed the naphthalene structure. Nearly all positive experiments with naphthalene lead to β-substitution, which in itself is most unusual. Thus, using methyl chloride in the cold about 10 per cent. of β-methylnaphthalene is obtained (347). With tetralin it is necessary to moderate the reaction by using aluminium bromide [3] when good yields of the β-ethyl (348) and β-*iso*propyl tetralins can be obtained. The entry of alkyl groups into the β-position of naphthalene and tetralin appears to be exactly comparable with the *m*-*p*-entry (and avoidance of *ortho*-position) in the case of benzene and its homologues. The use of dihalides and benzene leads to dihydroanthracenes; methylene dichloride and benzene give dihydroanthracene itself (349) and toluene gives a mixture of 2-methylanthracene, 1, 6-, 2, 7- and other dimethyl anthracenes. Diphenyl and methylene chloride yield fluorene. Many other examples of this type have been observed, and attention has already been drawn (see p. 169) to the reaction by which Anschütz obtained anthracene in an attempt to elucidate its structure, namely, the interaction of tetrachlorethane and benzene in the presence of anhydrous aluminium chloride. The use of alkylbenzenes and polyhalogenated aliphatic compounds often lead to very complex mixtures, since anhydrous aluminium chloride has an action on the individual components, apart from promoting their interaction, and, further, often has a rearranging action on the final products. Complex rings often ensue when aryl halogenides react with such rings as naphthalene, e.g., Gomberg [4] obtained an interesting fused ring fluorene derivative (351) from naphthalene and diphenyldichloromethane (350). It will be noted that the carbon atom marked with an asterisk is carrying a hydrogen



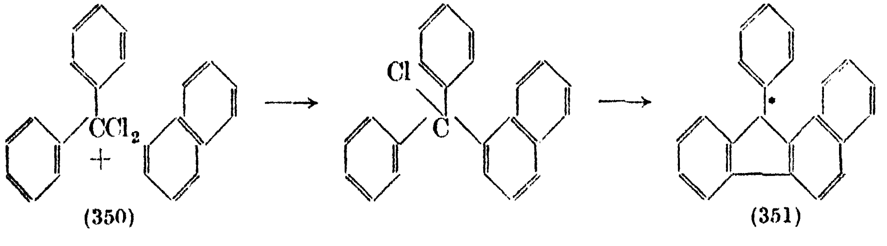
(347)



(348)



(349)



(350) (351)

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[1] U.S.P. 2,023,566 (1935).

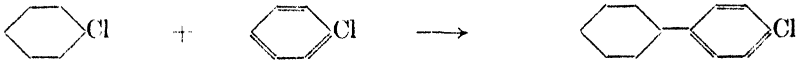
[2] Gerhardt, *Reichstoffind*, 1930, 5, 67.

[3] Barbot, *Bull. Chim. Soc.*, 1930, **4**, **47**, 1314.

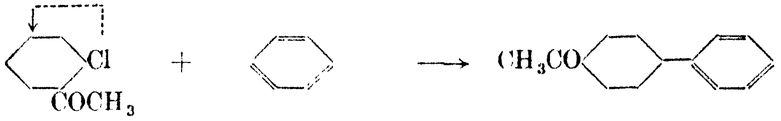
[4] Gomberg, *Ber.*, 1940, **37**, 1637.

atom in the final product, but in the initial raw material was attached to two rings and two chlorine atoms ; this shows that quite deep-seated changes may take place under the influence of anhydrous aluminium chloride, and that it is not safe to assume the structure of the final compound to be directly related to that of the reacting components.

The alicyclic halides react similarly to the alkyl compounds, although except in the simplest cases, migration of halogen may occur as preliminary to the Friedel-Crafts condensation proper. Thus, although *cyclo*hexyl chloride (352) and chlorobenzene react normally to give a good yield of 4-chlorophenyl*cyclo*hexane (353)[1] 2-chloro-1-aceto*cyclo*hexane (354) yields a *para*-derivative when reacting with benzene (355) from which it is assumed that under the influence of anhydrous aluminium chloride the halogen of the chloro-aceto compound migrates to the *para*-position.

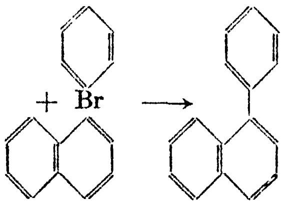


(352) (353)

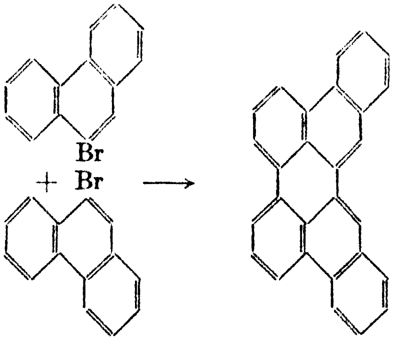


(354) (355)

When a halogen atom is attached to a benzene nucleus it is unusual for it to take part in a Friedel-Crafts synthesis with another aromatic residue. Exceptions are the reaction discovered by Chattaway of bromobenzene and naphthalene[2] in the presence of anhydrous aluminium chloride to give α-phenylnaphthalene (356). The converse reaction also proceed (namely, α-chloronaphthalene with benzene) but, surprising enough, β-chloronaphthalene also gives the α-phenylnaphthalene in reaction with benzene.[3] An interesting example of a condensed nuclear Friedel-Crafts reaction is the reaction of two molecules of 9-bromophenanthrene (357) in the presence of anhydrous aluminium chloride to give 2 : 3, 10 : 11-dibenzperylene (357*a*).[4]



(356)



(357) (357*a*)

The effect of substituent groups on the progress of the Friedel-Crafts reaction may be summarised thus :—

Aldehydes.—Chlorinated aldehydes give a mixture of substances with aromatic hydrocarbons and anhydrous aluminium chloride. Thus chloral gave some tetraphenylethane with a mixture of other compounds not identified. The method is not of great importance.

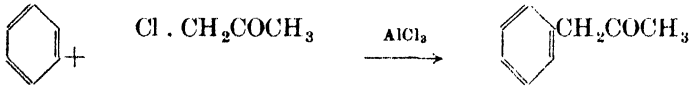
[1] Mayes and Turner, *J.C.S.*, 1929, 500.

[2] Chattaway, *ibid.*, 1893, **63**, 1185.

[3] Chattaway and Lewis, *ibid.*, 1894, **65**, 869.

[4] Clar, *Ber.*, 1932, **65**, 846.

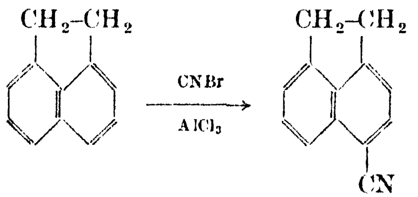
Ketones.—Chlorinated ketones such as chloroacetone, react normally with aromatic hydrocarbons in the presence of anhydrous aluminium chloride, e.g.,



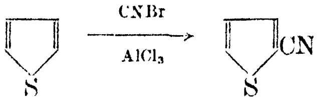
Phenylacetone

Ethers, on the other hand, do not react easily or normally. Thus, when chlormethylether reacts with benzene, diphenyl methane is produced.[1]

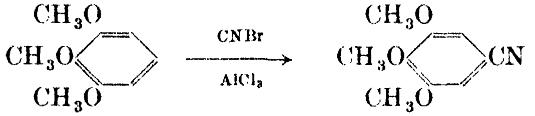
An unusual but valuable reaction is the action of cyanogen bromide with hydrocarbons in the presence of aluminium chloride to form nitriles. The reaction was thoroughly investigated by Karrer,[2] who observed that if the cyanogen bromide was fresh, good yields of nitriles were obtained, especially from condensed nuclei such as acenaphthene (358), and from thiophen (359) and the polymethoxybenzenes, e.g., 1, 2, 3-trimethoxybenzene (360).



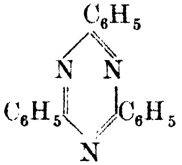
3-Cyanoacenaphthene
(358)



α-Cyanothiophen
(359)



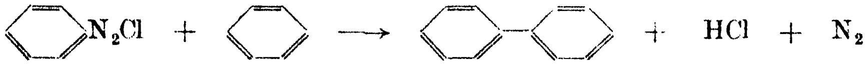
(360)



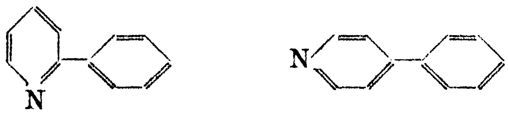
(361)

The condensation takes place also quite readily with cyanuric chloride; with benzene, cyaphenine (a neutral, white crystalline product) is formed (361), whilst with polynuclear hydrocarbons, e.g., phenanthrene, or with β-naphthol, products are obtained which can be used as dyestuffs.

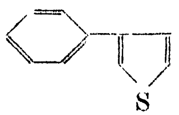
Aryldiazonium chlorides may also be induced to react with aromatic hydrocarbons in the presence of aluminium chloride when the principal products are bisaryl compounds, e.g., diphenyl :—



Whilst this reaction is of little value for making diphenyl, it can be utilised to obtain a variety of otherwise inaccessible substances[3] such as the phenylpyridines (362) and phenylthiophen (363).



α- γ-
(362)



(363)

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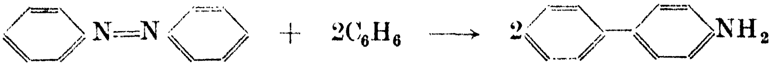
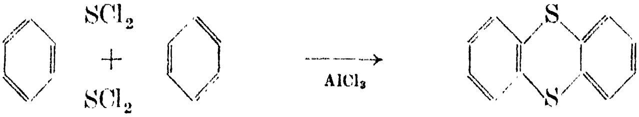
[1] Verley, *Bull. Soc. Chim.*, 1897, 3, **17**, 906.
[2] Karrer *et al.*, *H. Ch. Acta.*, 1919, **2**, 482 ; 1920, **3**, 261 ; Steinkopf, *Ann.*, 1923, **430**, 87.
[3] Mohlau and Berger, *Ber.*, 1893, **26**, 1196, 1994.

A variant of this reaction which is of practical importance is the large-scale production of xenylamine which is obtained in excellent (80 per cent.) yield by the interaction of azobenzene with benzene saturated with hydrogen chloride, using aluminium chloride as a promoter[1] :—

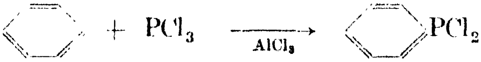


Sulphur halides and related compounds react with aromatic hydrocarbons in the presence of aluminium chloride. Thus, benzene, aluminium chloride and sulphur dichloride give thianthrene (364).[2]



(364)

Benzene, with thiophosgene or thiocarbonyl tetrachloride ($CCl_3 . SCl$) gives thiobenzophenone, a deep blue-green liquid.[3] Michaelis[4] applied the Friedel-Crafts reaction to the preparation of arylphosphine dichlorides, e.g., phenylphosphine dichloride (365); many examples of this series have been prepared by this method.

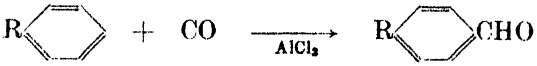


(365)

SYNTHESIS OF KETONES

One of the most successful applications of the Friedel-Crafts synthesis is the formation of ketones from aromatic hydrocarbons and acyl halides; the original Friedel-Crafts procedure (gradual addition of aluminium chloride to the acyl-halide diluted with the hydrocarbon) does not give very good yields, and Perrier's modification is worthy of note in increasing the yield considerably. Perrier dissolves the acyl halide in carbon disulphide, and treats the solution with aluminium chloride, thereby causing the formation of the double compound, which is then reacted with the hydrocarbon. In Table XXXIX will be found some notes on the various applications of this synthesis. In respect of the references given in the end column of this table, it may be added that only an occasional typical preparation is referred to (usually where the method is described in detail); the number of original communications dealing with ketone synthesis is very large (over nine hundred).

In general it may be said that acyl halides react with benzene and the fused ring benzenoid hydrocarbons consistently with the elimination of hydrogen chloride and the formation of the ketone. A very logical development of the Friedel-Crafts reaction is its extension to the synthesis of aldehydes by the use of carbon monoxide. This is often referred to as the Gatterman-Koch reaction. The net result of the reaction may be expressed thus :—



but the reaction, like many types of Friedel-Crafts synthesis, requires the presence of hydrogen chloride and an activator, usually cuprous chloride. The true intermediate is formyl chloride which reacts with the hydrocarbon in a normal Friedel-Crafts fashion :—

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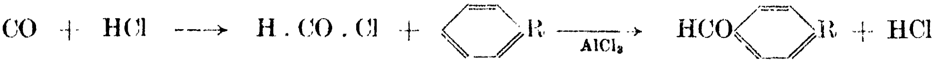
[1] Pummerer and Binapfl, *Ber.*, 1921, **54**, 2768.

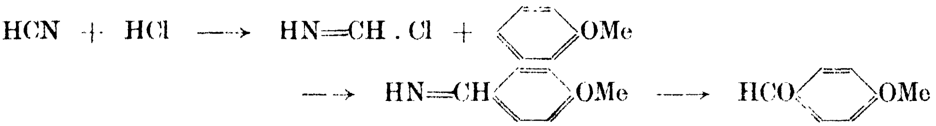
[2] Fries and Vogt, *Ann.*, 1911, **381**, 312.

[3] Bergreen, *Ber.*, 1888, **21**, 337 ; Vorlander and Mittag, *Ber.*, 1919, **52**, 413.

[4] Michaelis, *Ann.*, 1896, **293**, 193 ; 1896, **294**, 1 ; 1901, **315**, 43 ; *Ber.*, 1879, **12**, 1009. Michaelis and Panek, *Ann.*, 1882, **212**, 203 ; *Ber.*, 1880, **13**, 653.



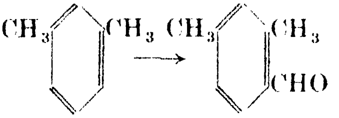
Thus, the reaction is maintained on the recycled hydrogen chloride. The modification of the Gattermann-Koch reaction, somewhat confusingly known as the Gattermann reaction,[1] uses hydrogen (or zinc) cyanide, hydrogen chloride and aluminium chloride, and depends for its activity on the iminoformyl chloride formed :—



It enables the synthesis to be extended to phenols and phenol ethers which are not amenable to the Gattermann-Koch reaction.[2] Some examples of substances produced by this reaction are shown below in outline :—

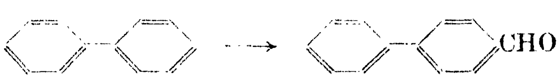
A. Gattermann-Koch.

(1)



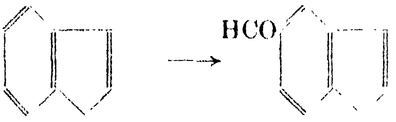
m-Xylene 2, 4-Dimethylbenzaldehyde [3]

(2)

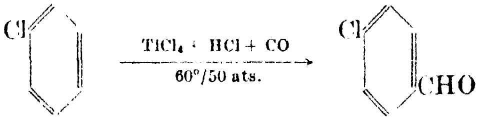


Diphenyl-4-aldehyde [4]

(3)

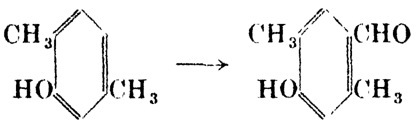


Hydrindene-5-aldehyde [5]

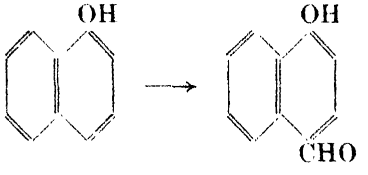


p-Chlorobenzaldehyde [6]

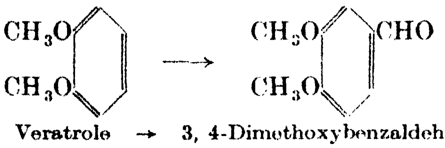
B. Gattermann.



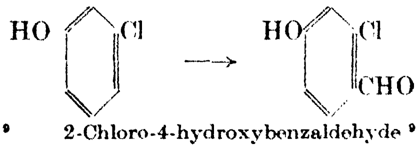
p-Xylenol 2, 5-Dimethyl-4-hydroxybenzaldehyde [7]



4-Hydroxy-1-naphthaldehyde [8]



Veratrole → 3, 4-Dimethoxybenzaldehyde [9]



2-Chloro-4-hydroxybenzaldehyde [9]

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[1] Gattermann *et al.*, *Ber.*, 1898, **31**, 1149 ; 1898, **31**, 1765 ; 1899, **32**, 278 ; 1899, **32**, 289.

[2] Gattermann and Koch, *ibid.*, 1897, **30**, 1622.

[3] Coleman and Craig, *Org. Syn.*, 1932, **12**, 80.

[4] Hey, *J.C.S.*, 1931, 2476.

[5] Gattermann, *Ann.*, 1906, **347**, 347.

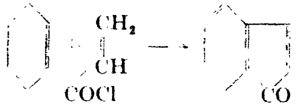
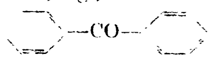
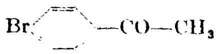
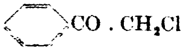
[6] U.S.P. 1,939,005 (1933).

[7] Gattermann, *Ann.*, 1907, **357**, 313.

[8] Gattermann and Horlacher, *Ber.*, 1899, **32**, 284.

[9] Gattermann, *Ann.*, 1907, **357**, 313.

TABLE XXXIX

Hydrocarbon	Acyl halide from—	Product	Comments
Aromatic, e.g., benzene	Simple monobasic acids Capryloyl chloride	Simple alkyl/aryl ketone *n*-Heptyl phenylketone	Proceeds as usual, even up to higher acid chlorides, such as stearoyl chloride Hartung *et al.*, *J.A.C.S.*, 1930, **52,** 3317
Aromatic, e.g., benzene	Unsaturated aliphatic acids	Indones are often formed, especially from acryloyl chloride : 	Kohler, *Am. Ch. J.*, 1909, **42,** 375
Aromatic, e.g., benzene	Aromatic acids, e.g., Benzoyl chloride	Diaryl ketones, e.g., 	Norris *et al.*, *Ber.*, 1910, **43,** 2940
Iodobenzene, bromobenzene or chlorobenzene	Aliphatic or aromatic acids	*p*-Halogeno aryl alkyl ketone, e.g., 	Straus and Ackermann, *Ber.*, 1909, **42,** 1812
Polyalkyl benzenes	Acids	The acyl group enters as follows — Alkyl benzene — Position 1, 2, *di*-, — 4 1, 3 *di*-, — 4 1, 4 *di*-, — 2 1, 3, 5 *tri*- — 2 1, 2, 4 *tri*- — 5 1, 2, 3, 4 *tetra*- — 5 1, 2, 4, 5 *tetra*- — 3	
Simple aromatic	**Halogenated aliphatic acids, e.g., $ClCH_2COCl$**	The halogen substituted alkyl/aryl ketone e.g., 	**Only the acyl halogen reacts, except in unusual conditions.** **Collet, *Bull. Soc. Chim.*, 1897 [3], 17, 506**

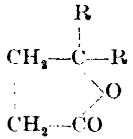
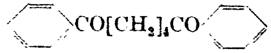
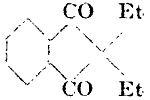
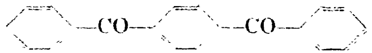
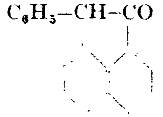
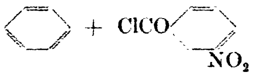
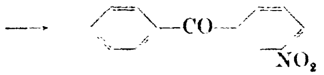
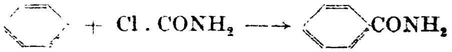
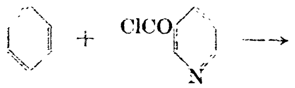
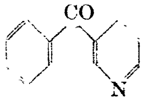
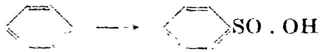
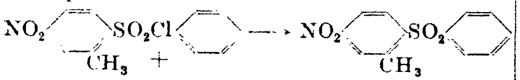
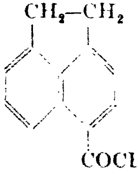
Benzene and homologs	Carbonic acid, i.e., Phosgene	Benzoyl chloride or benzophenone, and homologues	Both stages can be distinguished in the action Friedel *et al.*, *C.R.*, 1877, **85**, 673
Benzene and homologs	Dibasic acids, (oxalyl chloride is decomposed by $AlCl_3$) Succinic acid dichloride reacts mainly as the unsymmetrical compound	Oxalic acid gives benzoyl chloride and benzophenone Succinyl chloride gives 	Adipyl chloride and higher chlorides react normally to give  Malonyl chloride and its derivatives gives indandiones, e.g.,  Fuson and Walker, *Org. Syn.*, 1933, **13**, 32
Benzene and homologs	Aryl *o*- *m*- and *p*-dicarboxylic acids	React normally Give diketones of the structural type 	A tetracarboxylic acid from anthraquinone has been shown to react normally Limpricht, *Ann.*, 1898, **299**, 286 Scholl *et al.*, *Ann.*, 1934, **513**, 295
Naphthalene	Aromatic acids	Normal in α-position  (363*a*)	Some exceptions involving a *peri*-link are met with, e.g., attempts to induce phenyl- naphthacetyl chloride to react with benzene, led to 7-benzyl acenaphthone (363*a*) Koelsch and Richter, *J.A.C.S.*, 1937, **59**, 2165
Benzene and homologs	Nitrosubstituted aromatic acids 	Normal in most cases, e.g., 	The converse, e.g., benzoyl chloride on nitrobenzene does not proceed Montagne, *Rec. Trav. Chim.*, 1917, **36**, 260
Benzene and homologs	Carbamic acid $NH_2 . CO . Cl$	Normal	Benzamide is obtained almost quantitatively from benzene, carbamyl chloride  Gattermann, *Ann.*, 1888, **244**, 29

TABLE XXXIX (*continued*)

Hydrocarbon	Acyl halide from—	Product	Comments
Benzene and homologs	Pyridyl carboxylic acids and related compounds	Normal, e.g., nicotinyl chloride 	Wolffenstein and Hartwich, *Ber.*, 1915, **48**, 2043 
Benzene and homologs	Sulphur dioxide	Forms the sulphinic acids 	Good yields up to 80 per cent. Knoevenagel and Kenner, *Ber.*, 1908, **41**, 3315
Benzene and homologs	Sulphonic acids	Normal. Good yields of the sulphone are obtained	Example :  Ullmann and Lehner, *Ber.*, 1905, **38**, 729.
Naphthalene	Acids, generally	Normal, except for the peculiar influence of the solvents in determining the position of entry of substituents; with nitrobenzene the α-derivative is produced almost entirely; with bromonaphthalene as a solvent of the yield is mainly β-substituted	
Anthracene	Acids, generally	Normal; substituents enter the 1 and 2 positions in almost equal proportions, but if the conditions are mild the 9 acyl isomer is isolated	
Acenaphthene	Acids, generally	Is substituted normally in the 3 position, 	Graebe and Haas, *Ann.*, 1903, **327**, 96

In addition to the various reactions discussed, anhydrous aluminium chloride is able to bring about a variety of reactions, the chief of which are classified as

(1) Addition.
(2) Dehydration.
(3) Cyclic dehydrogenation.
(4) Polymerisation.

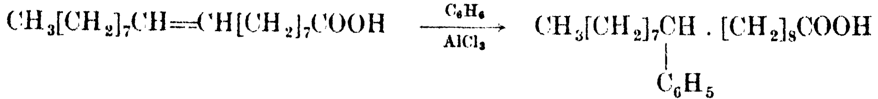
None of these may strictly be termed Friedel-Crafts reactions, although they are the logical development of the method originally worked out by Friedel and Crafts. For this and other reasons, it is convenient to consider them here.

The addition of aliphatic to aromatic hydrocarbons, in the presence of aluminium chloride, takes place with some reluctance in the case of acetylene and benzene, which give dibenzyl, together with a mixture of other products. On the other hand, ethylene reacts quite readily to give ethylbenzene, and if the passage of ethylene be continued the di-, and tri- and even hexa-ethylbenzenes are formed in good yield.[1] The reaction is a general one, and proceeds with long-chain normal olefines at least up to C_{16}. Certain types of branched chain ethylene derivatives are, however, cracked by the aluminium chloride, and give poly-substituted products, e.g., di-*iso*butene, benzene and aluminium chloride give di-*tert*-butylbenzene.

The extension of this reaction to naphthalenes, acenaphthenes, phenanthrenes and their partially hydrogenated products is described almost exclusively in the patent literature as the products have valuable wetting out or detergent properties. There is little published systematic work on this phase of Friedel-Crafts reaction.

The interaction of olefines with phenols and their ethers proceeds easily, and is the basis of a number of manufacturing procedures, especially for the manufacture of alkyl phenols, such as *tert*-butyl phenol, amylphenol and hexylphenol.

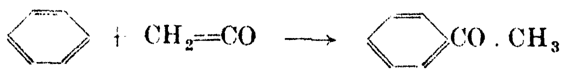
The addition may be carried out with unsaturated acids and aromatic hydrocarbons,[2] e.g., oleic acid gives 10-phenyloctadecane acid-1 (366).



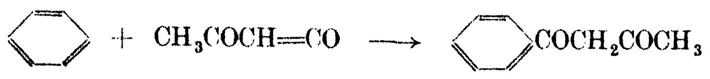
$$CH_3[CH_2]_7CH{=}CH[CH_2]_7COOH \xrightarrow[AlCl_3]{C_6H_6} CH_3[CH_2]_7\underset{\substack{|\\ C_6H_5}}{CH} . [CH_2]_8COOH$$

(366)

Hurd,[3] in his researches on the ketens, investigated their action on aromatic hydrocarbons, and obtained evidence of addition on the lines



the reaction did not appear to offer any advantage over, or even to compare in, yield, with the more usual methods of production. Diketen [4] was shown to give some benzoylacetone :—



The addition can take place intramolecularly, as in the case of 1-(α-naphthyl-2-(1-*cyclo*penten-1-yl)ethane (367) which [5] enables the synthesis of *cyclo*pentanophenanthrene derivatives to be accomplished ; in this case is 1, 2-*cyclo*pentano-1, 2, 3-4-tetrahydro phenanthrene (368). The reaction is general, and is one of paramount importance in the steroid field. It may be added that *cyclo*propane behaves somewhat unusually in that it adds to benzene, giving the *n*-propyl derivative.

---

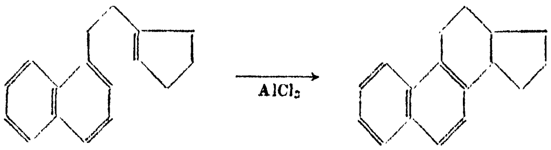
[1] Schleicher and Buttgenbach, *J. Pr. Chem.*, 1923, **105**, 355.

[2] Marcusson, *Z. Ang. Chem.*, 1920, **33**, 231.

[3] Hurd, *J.A.C.S.*, 1925, **47**, 2777.

[4] Hurd and Kelso, *ibid.*, 1940, **62**, 1548.

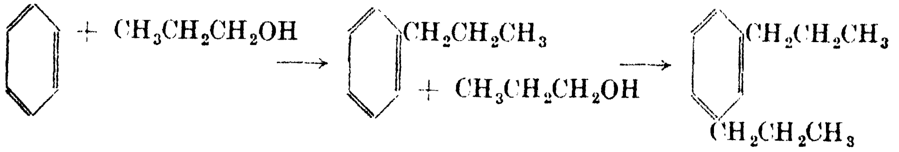
[5] Cook and Hewett, *J.C.S.*, 1933, 1098 ; Cook and Haselwood, *ibid.*, 1935, 767.

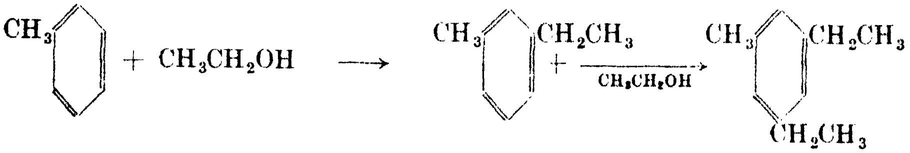


(367) (368)

Ethylene oxide can be induced to add to benzene, and if the latter be kept well in excess, a moderately good yield of phenylethanol can be obtained.[1] Within reason, the yield of alcohol increases with the proportion of benzene present.

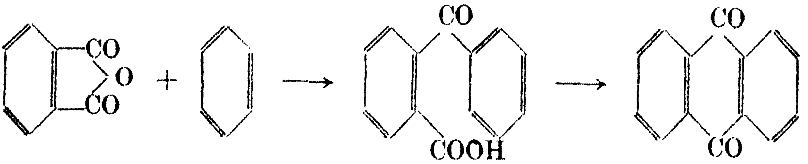
Dehydration Reactions.—It is only natural that the affinity which aluminium chloride has for moisture should make it a convenient dehydrating agent. It is probable, however, that hydrogen chloride plays a large part in the formation of the final compound. Tsukervanik and Vikhvova [2] obtained good yields of ethyl- and propyl substituted benzene and toluene from the appropriate hydrocarbon, and ethyl or propyl alcohol in the presence of aluminium chloride. It is significant that the substituents enters the *meta*-position, and that when working with a normal alcohol, a normal alkyl benzene is obtained, e.g. :—





Secondary and tertiary alcohols also react ; the reaction has been extensively investigated by Houston and his co-workers.[3]

The elimination of water from a molecule of a dicarboxylic acid anhydride and an aromatic compound is a reaction of fundamental importance. The reaction takes place in two stages, as indicated below, for benzene and phthalic



anhydride. As the presence of aluminium chloride is essential in the first step which is additive, but not for the second which, although actually accomplished in many instances by the aluminium chloride, can, in fact, be brought about by a variety of dehydrating agents, these reactions are often considered purely as additions.

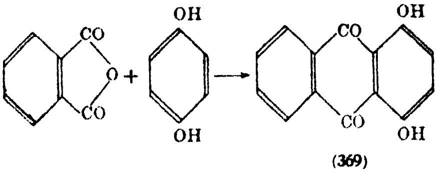
---

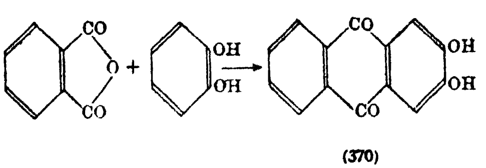
[1] U.S.P. 2,125,968 (1938).

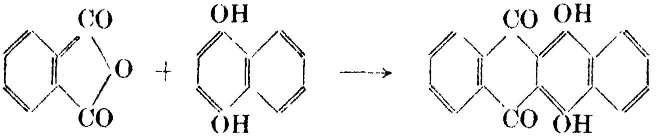
[2] Tsukervanik and Vikhvova, *J. Gen. Chem., U.S.S.R.*, 1937, **7**, 632.

[3] Houston *et al.*, *J. Org. Chem.*, 1938, **3**, 251 ; 1941, **6**, 652 ; *J.A.C.S.*, 1926, **48**, 1955 ; 1936, **58**, 439.

The reaction proceeds direct to the quinone more readily at higher temperatures and when the second reactant is a phenol, as for example in the synthesis of quinizarin (369) and hystazarin (370) from hydroquinone and catechol respectively :—

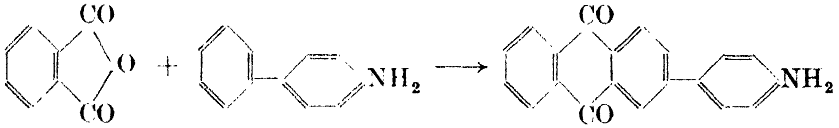

(369)


(370)

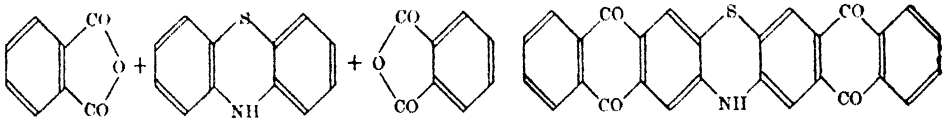

1, 4-Dihydroxy-2, 3-benzanthraquinone

and may be extended to dihydroxynaphthalenes.[1]

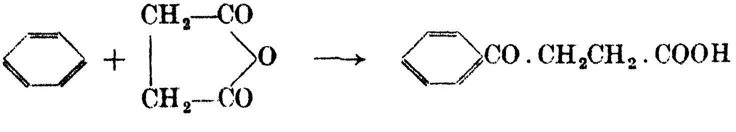
When sufficiently stable, arylamines containing two aryl residues, only one of which carries an —NH_2 group, will condense with phthalic anhydride, the


(371) (372)

simplest instance being phthalic anhydride and xenylamine (371), which give 2(4′-aminophenyl)-anthraquinone (372), and the method is capable of giving products of great complexity as, for example, when two molecules of phthalic anhydride (373) condense with phenothiazine to give 2, 3 ; 6, 7-diphthalylphenothiazine (374).


(373) (374)

As this reaction is also given by substituted phthalic anhydrides, its potentialities are thereby increased ; and in the case of tetrachlorophthalic anhydride, reaction takes place with such bodies as nitrobenzene and dichlorobenzene, with which the unsubstituted anhydrides do not react. The possible variants with this reaction are extremely numerous, and representatives of almost every type of structure can be prepared by its use ; it is extensible to succinic acid which reacts with benzene thus[2] :—



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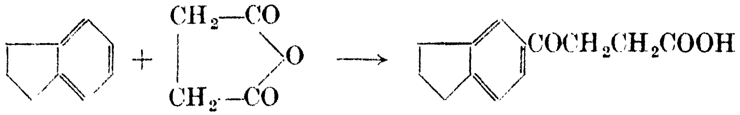
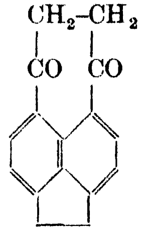
[1] Raudnitz, *Ber.*, 1929, **62**, 509.

[2] Kohler and Engelbrecht, *J.A.C.S.*, 1919, **41**, 764.

and condensed rings behave likewise,[1] e.g. :—

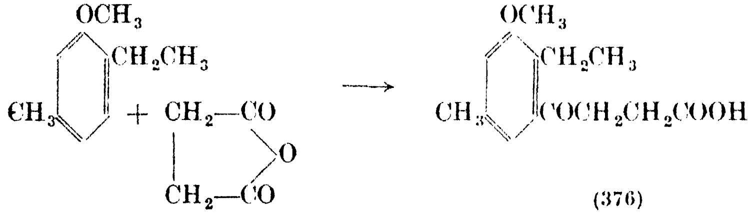


Hydrindene 1-(5-hydrindenyl)butanone-1-acid-4



(375)

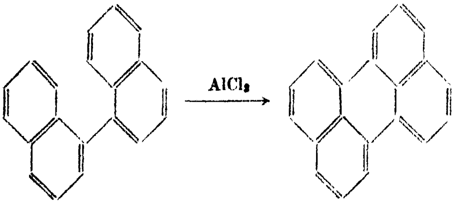
On the other hand, the peculiarly active 3, 4 positions in acenaphthene lead to the *peri-* succinoyl derivative (375). The condensation is particularly valuable in building up the 4-carbon substituted phenolic ethers, e.g., β-(3-methyl-6 ethylanisoyl)propionic acid (376)[2] :—



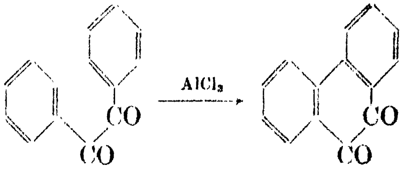
(376)

Dehydrogenating Reactions

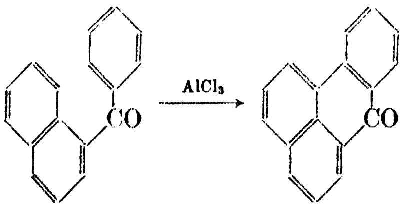
Reference has already been made in the section on hydrocarbons to the use of aluminium chloride for ring closure by dehydrogenation. We owe much of our knowledge of this reaction to the patient researches of Scholl, who in 1910[3] obtained perylene (378) from 1, 1′-dinaphthyl (377) by baking it with aluminium chloride. This development of the Friedel and Crafts reaction is frequently referred to as ' Scholl's reaction '.



(377) (378)



(379)



(380) (381)

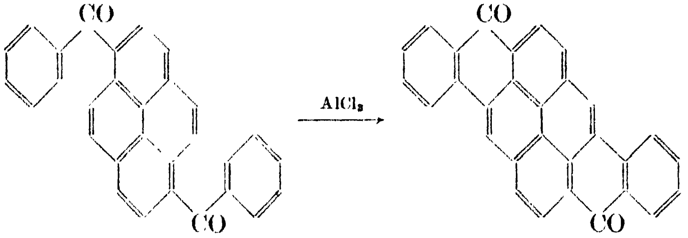
Perhaps the simplest instances are the formation of phenanthrenequinone from benzil (379) and the formation of 9-benzanthrone (381) from α-benzoylnaphthalene (380). The extensions of the reaction to give very complex

[1] Fieser and Seligman, *J.A.C.S.*, 1937, **59**, 883.

[2] Rice, *ibid.*, 1924, **46**, 2319.

[3] Scholl and Seer, *Monatsh.*, 1912, **33**, 1.

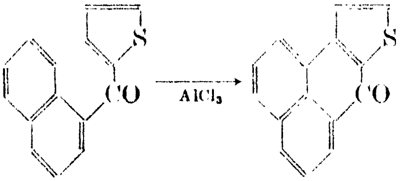
quinones have proved valuable in the production of light-fast vat dyes. In general, the principle involved is the production of a dibenzoyl derivative of a condensed benzenoid structure, followed by a Scholl reaction for completing the network. An example is the formation of pyranthrone (383) from dibenzoyl pyrene (382).



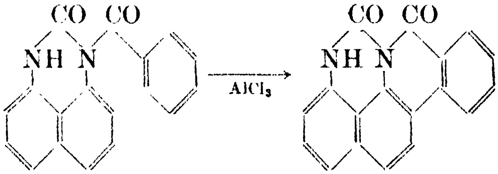
(382) (383)

Examples of this reaction abound in the patent literature, since the end-products are largely dyestuffs. Some instances involving principles other than those of simple ring closure in homocyclic compounds are :—

(1) The conversion [1] of 1-thienyl-1′-naphthyl ketone (384) to benzthiophanthrone-9 (385).



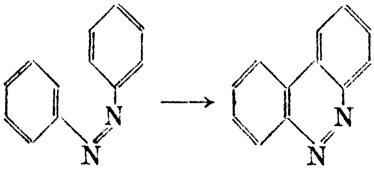
(384) (385)



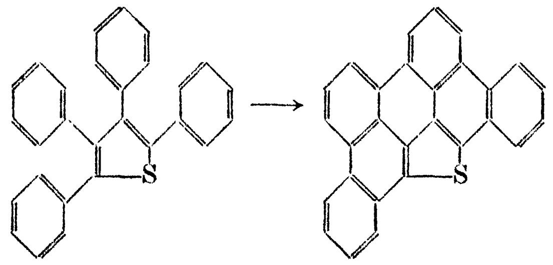
(386)

(2) The conversion [1] of benzoyl perimidone to the cyclic structure (386). The two examples given above indicate that the reaction proceeds with sulphur and nitrogen ring compounds.

(3) Azobenzene gives 3, 4-benzoquinazoline 9, 10-phenanthroline



(4) An interesting instance of the ubiquity of this reaction is the demonstration by Steinkopf [2] that tetraphenylthiophene (387) gives a dehydro-α-diphenanthrenothiophene (388) by Scholl's reaction.

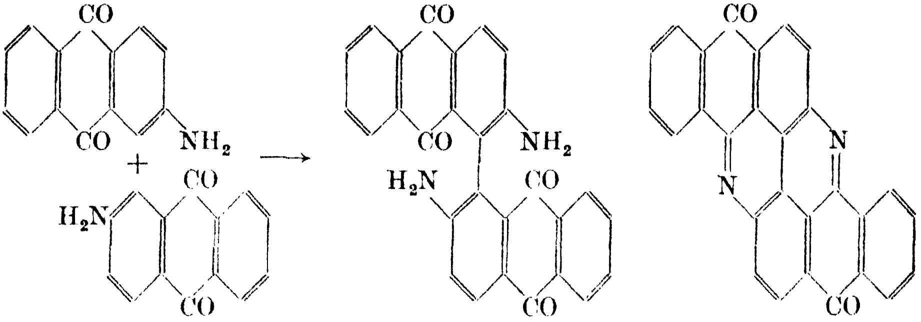


(387) (388)

[1] U.S.P. 1,749,955 (1930).

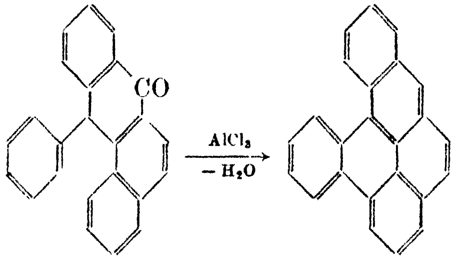
[2] Steinkopf, *Ann.*, 1935, **519**, 297.

(5) It is not essential that the two parts of the final molecule be joined before applying Scholl's reaction ; in many cases the first link is made under the influence of aluminium chloride. Thus, when 2-amino-anthraquinone (389) is heated with aluminium chloride, flavanthrone (391) is obtained *via* the diamino-dianthraquinoyl first formed [1] (390) :—



(389) (390) (391)

(6) It will have been observed that in the instances quoted above, ring closure takes place with the elimination of one molecule of hydrogen. This hydrogen has, of course, to find an acceptor, which in many cases is the keto group, which becomes converted to $>$CHOH. This accounts for the fact that in leaching out the melt from a Scholl reaction, the product often dissolves as a species of leuco-compound and the highly coloured quinone is only obtained on aerial oxidation of the hydrol. Another consequence of this fact is that where the bond structure allows, the quinone group may be completely reduced with the elimination of water, as when phenyl-1-naphthylphthalide (392) is submitted to the Scholl reaction ; here, the product is not a ketone,[2] but the hydrocarbon 1, 2, 3, 4-dibenzpyrene (393).



(392) (393)

MECHANISMS OF THE FRIEDEL-CRAFTS REACTION

In 1877, when Friedel and Crafts discovered the reaction between benzene, anhydrous aluminium chloride and alkyl halides, they visualised the action as taking place :—

$$C_6H_6 + Al_2Cl_6 \longrightarrow C_6H_5 . Al_2Cl_5 + HCl$$
$$C_6H_5 . Al_2Cl_5 + R . Cl \longrightarrow C_6H_5R + Al_2Cl_6$$

They were, however, unable to detect the formation of the substance $C_6H_5 . Al_2Cl_5$. Two years later Gustavson [3] isolated some true addition compounds between benzene or toluene and aluminium chloride or bromide which he formulated :—

$$Al_2Br_6 . 6[C_6H_6]$$

---

[1] Clar, *Ber.*, 1930, **63**, 112.

[2] Clar, *ibid.*, 193, **63**, 112.

[3] Gustavson, *Bull. Soc. Chim.*, 1879,2, **31**, 71 ; *Ber.*, 1878, **11**, 21510 ; 1879, **12**, 853.

It was not at the time clear whether these complexes played a part in the Friedel-Crafts synthesis or not.

Recently Norris and co-workers[1] have reinvestigated the matter, and have established the fact that these complexes need the halogen acid for their formation, but that the formulation of Gustavson, sixty years previously, had been substantially correct. On the other hand, it had already been demonstrated that alkyl halides (e.g., ethyl bromide) formed complexes with aluminium chloride by loss of hydrogen halide, e.g.,

$$Al_2Cl_6 + 4C_2H_5Br \longrightarrow 4HBr + Al_2Cl_6 \cdot C_8H_{16}$$

These additional products would themselves react with aromatic hydrocarbons :—

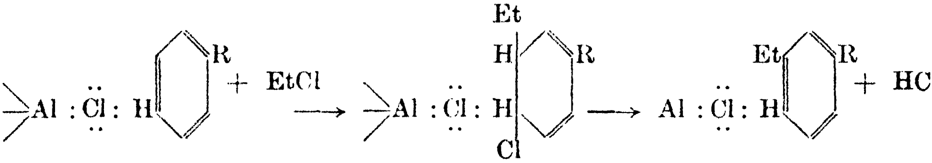
$$Al_2Cl_6C_8H_{16} + 6C_6H_6 \longrightarrow Al_2Cl_6 \cdot C_8H_{16} \cdot [C_6H_6]_6.$$

This ternary complex is dissociated into its molecular components by heat, but will react with ethyl bromide to form a new ternary product,

$$Al_2Cl_6 \cdot C_8H_{16}[C_6H_3Et_3]_6,$$

i.e., a complex in which *s*-triethylbenzene has replaced the benzene of the former. The action of heat on this new complex is, as before, to dissociate it into its components, but the precise mechanism by which the benzene becomes ethylated is no clearer.

Schaarschmidt, in attempting to elucidate the mechanism of alkylation postulates a complex of aluminium halide, hydrocarbon and alkyl halide, the latter being held by normal valencies and the aluminium chloride through auxiliary valencies. This would involve a sequence of structures such as :—

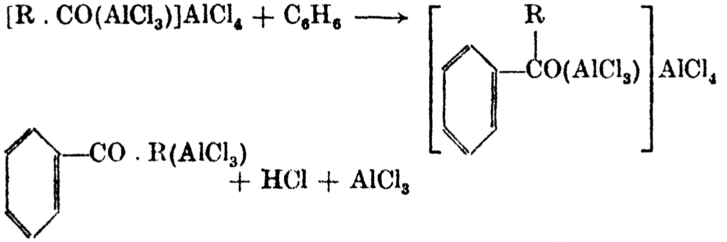


(394) (395) (396)

This could be visualised as if each chlorine atom of the $Al_2Cl_6 \cdot C_8H_{16}$ complex associated with a hydrogen atom of a benzene ring as in (394), thereby so loosening the second Kekulé pair as to allow addition to (395), followed by loss of hydrogen chloride to give the structure (396). This would explain the fact that in the vast majority of Friedel-Crafts reactions the new substituent enters a position *meta-* to the existing one.

A similar sequence has also been postulated by Dilthey,[2] who in the case of benzyl chloride postulates a complex, $[C_6H_5CH_2]AlCl_4$, which is capable of activating one of the double bonds of the second aromatic structure sufficiently to allow of addition. Dilthey has extended his explanation to cover the ketone syntheses by the following sequence :—

$$R \cdot COCl + Al_2Cl_6 \longrightarrow [R \cdot CO(AlCl_3)]AlCl_4$$



It is difficult to regard this as much more than a symbolised restatement of the facts of complex formation and Friedel-Crafts synthesis.

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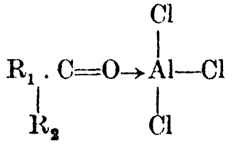
[1] Norris *et al.*, *J.A.C.S.*, **1939, 61,** 1163 ; 1940, **62,** 1298 and 1428.

[2] Dilthey, *Ber.*, **1938, 71,** 1350.

Dynamic investigations of the Friedel-Crafts reaction were made by Steele,[1] Olivier,[2] and Martin,[3] but without shedding much light on the precise mechanism involved. It is, however, quite clear that one school of thought favours an explanation of the Friedel-Crafts reaction which involves the use of the *complex* as a factor in loosening the bonds in benzene sufficiently to enable addition and elimination of hydrogen halide.

Another view is that these complexes do not take an active part in the reaction. It can be demonstrated that the majority of substances containing the =CO group form complexes with aluminium chloride of the type (397).

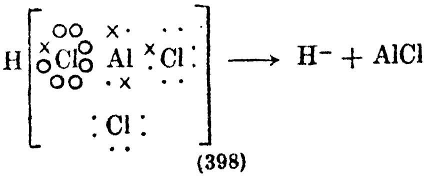


$$\begin{array}{l} \qquad\qquad\qquad\quad Cl \\ \qquad\qquad\qquad\quad | \\ R_1 . C{=}O{\rightarrow}Al{-}Cl \\ \;| \qquad\qquad\quad\; | \\ R_2 \qquad\qquad\;\; Cl \end{array}$$

(397)

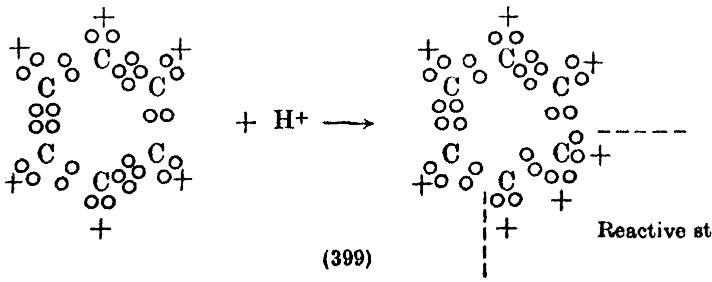
The strength of attachment of the two parts of such a molecule may be such as permanently to withdraw the attached aluminium chloride from the reaction. This is particularly marked in the case of ketones where, for example, considerably more aluminium chloride must be used in the synthesis of acetophenone from benzene and acetyl chloride, than is necessary for the formation of ethylbenzene from benzene and ethyl chloride. There is, however, according to Thomas,[4] doubt as to whether these complexes play any part in the reaction *per se*, other than determining the amount of aluminium chloride required.

There is a general consensus of opinion that hydrogen chloride is essential for all aluminium chloride syntheses; reactions in which the reactants are made anhydrous, and in which aluminium chloride is dry and free from hydrogen chloride proceed slowly or not at all; aluminium chloride which has been heated in a current of hydrogen chloride is more active than that which has not been so treated. It has been assumed, therefore, that hydrogen chloride and aluminium chloride react to form the complex (398) which can ionise [5] to give the proton and a stable $AlCl_4$ ion, thus :—



(398)

This proton is held to be responsible for setting the benzene ring into an unstable state (399), making it reactive itself towards the alkyl or acyl chloride :—



(399)

Reactive state.

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[1] Steele, *Pr. Chem. Soc.*, 1930, **19**, 209; *J.C.S.*, 1903, **83**, 1470.

[2] Olivier, *Rec. Trav. Chim.*, 1918, **37**, 205; 1935, **54**, 943.

[3] Martin *et al.*, *J.A.C.S.*, 1935, **57**, 2584.

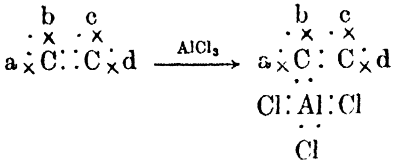
[4] Thomas, "Anhydrous Aluminium Chlorine in Organic Chemistry", A.C.S. Monograph o. 87.

[5] Ipatiev *et al.*, *J. Org. Chem.*, 1940, **5**, 253.

It is held that the disruptive effect of aluminium chloride on aliphatic hydrocarbons proceeds by means of the activated proton from $H[AlCl_4]$, which captures an electron pair from a carbon link, and thus leads to a type of reaction which it is difficult to visualise happening in any other way :—

$$\left\downarrow\begin{array}{l} CH_3[CH_2]_6CH_2 \,.\, CH_2[CH_2]_6CH_3 + H^+ \\ CH_3[CH_2]_6CH_3 + {}^-CH_2 \,.\, [CH_2]_6CH_3 \\ CH_3[CH_2]_6CH_3 + CH_2{=}CH \,.\, [CH_2]_5CH_3 + H^+ \end{array}\right.$$

The general position may be summarised as follows. In the Friedel-Crafts reaction a disturbance of the structure of the aromatic hydrocarbon takes place which enables addition to take place followed by formation of a substituted hydrocarbon. It is not clear whether this activation is due to a loose combination between the hydrocarbon and a proton from $H[AlCl_4]$, or between the hydrocarbon and the chlorine from an (Al_2Cl_6 Alkyhalide) type of complex. Both these explanations depend fundamentally on the electron shortage of aluminium chloride ($AlCl_3$). Nenitzescu [1] applies this theory of electron shortage of aluminium chloride to explain its action on unsaturated hydrocarbons, which thus becomes analogous to the catalytic action of boron trifluoride. The complex between aluminium chloride and unsaturated hydrocarbons is written thus :—



$$a\,{}^{\cdot}_{\times}\overset{\substack{b\\ \cdot\times}}{C}{:}{:}\overset{\substack{c\\ \cdot\times}}{C}\,{}^{\cdot}_{\times}d \xrightarrow{AlCl_3} a\,{}^{\cdot}_{\times}\overset{\substack{b\\ \cdot\times}}{\underset{\substack{\cdot\cdot\\ Cl:Al:Cl\\ \cdot\cdot\\ Cl}}{C}}:\overset{\substack{c\\ \cdot\times}}{C}\,{}^{\cdot}_{\times}d$$

(400)

leaving in (400) a carbonium, or six-electron, carbon which is sufficiently active to attack an unsaturated bond as in benzene, or to give polymerisation in the absence of an addend.

---

[1] Nenitzescu, *Ang. Chem.*, 1939, **52**, 231.

CHAPTER IV

HALOGEN COMPOUNDS OF HYDROCARBONS

In this chapter are considered all those substances obtainable by the substitution into a hydrocarbon structure of one or more atoms of fluorine, chlorine, bromine and iodine. It will be clear that whatever remarks have been made in previous chapters concerning the multiplicity of theoretical structures, apply *a fortiori* to the halogen substituted hydrocarbons. The numerical possibilities of this family have been worked out by Blair,[1] who points out, for instance, that there are 1553 possible isomers even for so simple a substance as $C_{10}H_{21}Br$. Blair's figures for the stereoisomeric and non-stereoisomeric monohalogen hydrocarbons are given in Table I.

TABLE 1

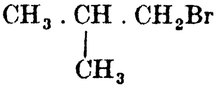
No. of Carbon Atoms	1	2	3	4	5	6	7	8	10	12	15	20
No. of isomers	1	1	2	5	11	28	74	199	1553	12,832	328,092	82,299,275

It is convenient to divide the saturated halogen compounds into three classes, primary, secondary and tertiary, according to the number of carbon atoms attached to the carbon atom carrying the halogen. This is illustrated by the four isomeric butyl bromides, two of which are 'primary'. There is a pronounced difference in behaviour between the various types of primary halides, and also between the methods by which they can be produced.

$CH_3 . CH_2 . CH_2 . CH_2Br$

(1)

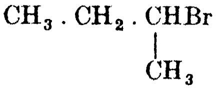
primary



$CH_3 . \underset{\displaystyle CH_3}{CH} . CH_2Br$

(2)

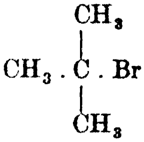
primary



$CH_3 . CH_2 . \underset{\displaystyle CH_3}{CHBr}$

(3)

secondary



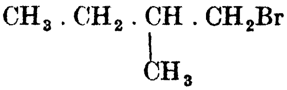
$CH_3 . \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} . Br$

(4)

tertiary

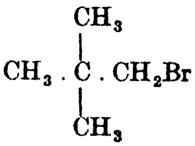
$CH_3CH_2CH_2CH_2CH_2Br$

(5)



$CH_3 . CH_2 . \underset{\displaystyle CH_3}{CH} . CH_2Br$

(6)



$CH_3 . \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} . CH_2Br$

(7)

Thus, all three amyl bromides shown (5) to (7) are primary, but differ considerably in respect of the lability of the halogen atom and the ease of production; *n*-amyl bromide (1-bromopentane) (5) is readily obtained pure by distillation of a mixture of the corresponding amyl alcohol and concentrated hydrobromic acid; the isomeric 1-bromo-2-methyl butane (6) is best obtained from the corresponding amyl alcohol by the action of phosphorus tribromide; even so, part of the product will be the tertiary bromide (8) or 2-bromo-2-methyl butane.

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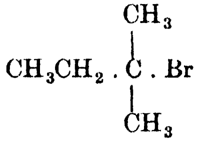
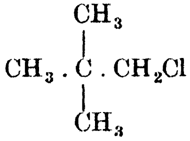
[1] **Blair and Henze, *J.A.C.S.*, 1932, 54, 1098.**



$$CH_3CH_2 . \overset{CH_3}{\underset{CH_3}{C}} . Br$$

(8)

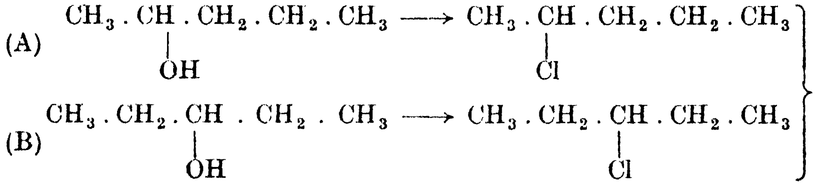


$$CH_3 . \overset{CH_3}{\underset{CH_3}{C}} . CH_2Cl$$

(9)

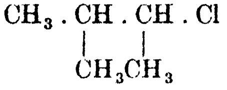
The third isomer (7) is almost impossible to produce, as any attempt to obtain it from the corresponding alcohol leads to a mixture of secondary and tertiary halides from which no primary halide can be obtained. The only representative of this series known is the corresponding chloride (9) which is obtained by the direct chlorination of the hydrocarbon neopentane.

This isomerisation during formation is common to the whole series and has been closely studied by Whitmore.[1] It may be illustrated by a short consideration of other members of the $C_5H_{11}Cl$ series. Thus, reaction of the corresponding alcohols with reagents calculated to replace the hydroxyl group by halogen, might be expected to proceed according to (A) and (B) below :—



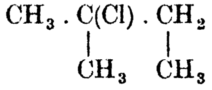
$$\left.\begin{array}{ll}(A) & CH_3 . \underset{OH}{CH} . CH_2 . CH_2 . CH_3 \longrightarrow CH_3 . \underset{Cl}{CH} . CH_2 . CH_2 . CH_3 \\ (B) & CH_3 . CH_2 . \underset{OH}{CH} . CH_2 . CH_3 \longrightarrow CH_3 . CH_2 . \underset{Cl}{CH} . CH_2 . CH_3\end{array}\right\}$$

in practice a mixture of the 2- and 3-chloropentanes is obtained, together with some secondary halides, whichever secondary alcohol is used, and even now there is some doubt as to which of the main products is 2-chloro- or 3-chloropentane. Further, any attempt to obtain the secondary chloride (10) from the corresponding alcohol leads only to the tertiary halide (11). Amongst



$$CH_3 . \underset{CH_3}{CH} . \underset{CH_3}{CH} . Cl$$

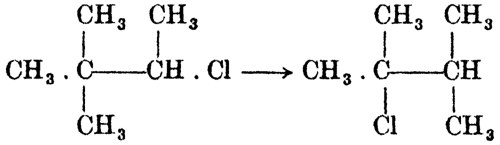
(10)



$$CH_3 . \underset{CH_3}{C(Cl)} . \underset{CH_3}{CH_2}$$

(11)

the higher homologues, secondary halides of the type (12) have never been obtained, the tertiary halide (13) always appearing. This protean tendency



$$CH_3 . \overset{CH_3}{\underset{CH_3}{C}}\text{——}\overset{CH_3}{CH} . Cl \longrightarrow CH_3 . \overset{CH_3}{\underset{Cl}{C}}\text{——}\overset{CH_3}{\underset{CH_3}{CH}}$$

(12) (13)

amongst the halides complicates their study, and in the absence of a simple method of determination of structure, this group has become one of the least studied sections of organic chemistry.

There are three main methods by which halides may be obtained :—

(1) By direct halogenation of the hydrocarbon.
(2) By addition of a halogen or halogen acid to an unsaturated hydrocarbon.
(3) By conversion of an oxygenated compound—an alcohol, aldehyde or ketone to the mono- or di-halogen derivative with halogen acids, phosphorus halides, thionyl chloride or similar reagents.

---

[1] Whitmore *et al.*, *J.A.C.S.*, 1933, **55**, 812; *J.C.S.*, 1934, 1269.

Fluoro- Compounds

The reactions set out above are generally unsatisfactory for the production of fluorine derivatives for which special methods are required. The action of fluorine on hydrocarbons is violent and often leads to a breakdown of the hydrocarbon to carbon and hydrogen. Even when the hydrocarbon is not wholly destroyed the variety of compounds formed is sufficient to make their separation extremely difficult. Again, hydrofluoric acid does not add to double bonds under normal conditions, and fluoro derivatives of the aliphatic series are produced mainly by interchange reactions such as

$$C_2H_5I + AgF \longrightarrow C_2H_5F + AgI.$$

Exchanges can be made between chlorine and fluorine when antimony trifluoride reacts with polychloro hydrocarbons in the presence of antimony pentachloride. Thus, antimony trifluoride and carbon tetrachloride yield difluorodichloromethane, CCl_2F_2, which finds application under the name 'Freon' as a refrigerant.

$$3CCl_4 + 2SbF_3 \xrightarrow[SbCl_5]{} 3CCl_2F_2 + 2SbCl_3.$$

An extension of the reaction above is the interaction of carbon tetrachloride and hydrogen fluoride in the presence of antimony pentachloride present in catalytic quantities.

$$CCl_4 + 2HF \xrightarrow{SbCl_5} CCl_2F_2 + 2HCl.$$

It is interesting to note that the use of difluorodichloromethane in refrigeration is an example, almost unique, of the production of a 'made-to-measure' organic substance, rather than of the application of a well-known substance in a new capacity.

Midgley and Henne [1] set out on paper the desirable properties of an ideal refrigerant. It should, of course, have certain thermodynamic properties, a latent heat of evaporation not lower than 25 calories per gram. It should boil at approximately − 30°, and its freezing point should be much lower; it should be unreactive, insoluble in water, odourless, non-toxic, non-corrosive and incapable of generating corrosive acids when in contact with water. It should be non-inflammable and chemically stable. One has only to recall the properties of ammonia and sulphur dioxide, the hitherto most widely used refrigerants, to realise how far they fall short of the ideal substance. Indeed, it seemed scarcely probable that all these properties could be combined in any single substance. A search of the literature, however, revealed that difluorodichloromethane had been prepared in small quantity in Holland by Swarts,[2] and had at least some of the desirable properties. Repetition of Swarts' work on a larger scale showed difluorodichloromethane to have the following properties :—

TABLE II

Properties of Difluorodichloromethane, CF_2Cl_2

Appearance.	Colourless, odourless.
Physical properties.	B.p., — 30° ; m.p., — 155° ; density 1·40 — 0·00326*t*. Cp = 0·224 (liquid) ; Cp = 0·15 (vapour). Latent heat of vaporisation, 33·9 cal./gm. at — 30°.
Chemical properties.	Inert; insoluble in water, non-inflammable and has pronounced fire-extinguishing properties, e.g. butane mixed with twice its weight of difluorodichloromethane is non-inflammable. Without action on most substances when dry. In the presence of water attacks zinc and magnesium.

---

[1] Midgley and Henne, *Ind. Eng. Chem.*, **22**, 542.

[2] Swarts, *Bull. Acad. roy. Belg.*, **1907**, **339**.

Physiological properties. Inert; almost non-toxic; air containing 40 per cent. of difluorodichloromethane can be breathed for several hours without danger to life (compare the corresponding figures of 0·01 per cent. for ammonia and 0·1 per cent. for methyl chloride).

In short, difluorodichloromethane has all the properties desired,[1] and it only remained for its production to be carried out on an industrial scale. In spite of the fact that no organic fluorine compound had been obtained in industrial quantities previously, the manufacture of difluorodichloromethane was achieved by the methods indicated above, in which the yields approach 94 per cent. of the theoretical figure.

The alkyl fluorides are little known; methyl fluoride is a colourless gas, b. − 78°, whilst ethyl fluoride boils at − 32° and *n*-propylfluoride at − 2°; normal hexyl, heptyl and octyl fluorides boil at 85°, 119° and 142° respectively. Of the unsaturated fluorides, vinyl fluoride has been obtained as a stable gas, b. − 51°.

These substances are somewhat unexpectedly soluble in water. They may be prepared

(*a*) by the action of the iodide on silver fluoride,

(*b*) by heating tetralkyl ammonium fluoride, e.g.

$$[(CH_3)_4N]F \longrightarrow CH_3F + N(CH_3)_3,$$

(*c*) by heating together potassium alkyl sulphate with potassium fluoride, e.g.

$$KF + C_2H_5KSO_4 \longrightarrow K_2SO_4 + C_2H_5F.$$

Little or nothing is known concerning methylene difluoride and attempts to prepare fluoroform, CHF_3, by interaction of chloroform and antimony fluoride have led only to the partial substitution of fluorine for chlorine, as in $CHClF_2$, a colourless gas, b. − 40°, and, like the simple alkyl fluorides, easily soluble in water without hydrolysis.[2]

Fluoroform can, however, be prepared by heating bromoform and antimony pentafluoride. It is a colourless gas, b. − 82°, without marked chemical or physiological activity.

Carbon tetrafluoride is one of the most stable and inert of organic halides. It is a colourless gas, b. − 130°, m.p. − 191°, and was accidentally prepared by LeBeau by electrolysing fused potassium hydrogen fluoride with graphite electrodes;[3] at the same time numerous carbon fluorides are formed, including C_2F_6, b. − 79°[4], C_3F_8, C_4F_{10}, C_5F_{12}.

It is interesting at this point to note that on treating benzotrichloride with silver fluoride, benzotrifluoride is obtained:—

$$C_6H_5 \,.\, CCl_3 + 3AgF = C_6H_5 \,.\, CF_3 + 3AgCl.$$

When benzotrifluoride is oxidised the benzene ring is destroyed and trifluoracetic acid, CF_3COOH, an intensely stable substance, remains.

Aryl fluorides may be obtained by diazotising an arylamine and running the cooled diazo solution into hydrofluoric acid of 65–70 per cent. strength;[5] it is advantageous to use dilute sulphuric acid to dissolve the amine. In many cases it has been recommended that the fluoro compound be obtained by heating the diazonium fluoroborate obtained by dissolving the amine in fluoroboric acid and diazotising the solution ;[1] the diazonium fluoroborate separates and may be washed, dried and decomposed, e.g. :—

---

[1] Thompson, *Ind. Eng. Chem.*, 1932, **24**, 620.

[2] Henne, *J.A.C.S.*, 1937, **59**, 1400.

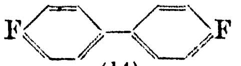
[3] Simon and Block, *ibid.*, 1937, **59**, 1407: 1939, **61**, 2962.

[4] Swarts, *Bull. Acad. roy. Belg.*, 1934, **20**, 782.

[5] Hollemann and Beckman, *Rec. Trav. Chim.*, 1904, **23**, 232.

$$\begin{array}{l} C_6H_5NH_2 + HBF_4 + HNO_2 \longrightarrow C_6H_5N_2[BF_4] \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad C_6H_5F + N_2 + BF_3. \end{array}$$

The fluoroboric acid method offers little advantage over the use of concentrated hydrofluoric acid, except in one or two special instances. In contradistinction to the other diazo/halogen replacements, the presence of copper affects the reaction adversely. Many fluorine substituted aryl compounds have been made by these methods for experimental purposes ; they are not of outstanding interest—their physical properties are usually very similar to those of the parent hydrocarbon, e.g. fluorobenzene is a colourless liquid, b. 85°, and very similar in odour and general properties to benzene itself. *p*-Difluorobenzene is a similar liquid, b. 88°. 4, 4′-Difluorodiphenyl (14) was at one time sold in the drug trade, as it was thought to have a beneficial effect in phthisis ; it has not, unfortunately, proved of real value in this connection.



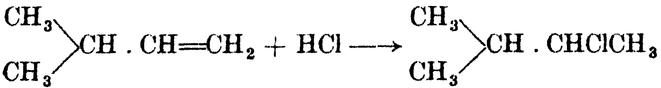
(14)

MONOCHLORO- COMPOUNDS

The formation of alkyl chlorides, such as the simple monochloro- paraffins, by direct entry of chlorine into a paraffin, has already been discussed (p. 75). The method is not suitable for the production of pure substances except in rare instances such as the chlorination of neopentane, where no ambiguity or isomerism can occur ; indeed, direct chlorination is the only suitable method for obtaining neopentyl chloride (1-chloro-2, 2-dimethyl propane) (9).

$$CH_3 . C(CH_3)_2CH_3 + Cl_2 \longrightarrow CH_3 . C(CH_3)_2CH_2Cl + HCl.$$

It is unusual to find the addition of hydrogen chloride to an unsaturated ethylene derivative a suitable method for arriving at an alkyl chloride, although in the case of 3-chloro-2-methylbutane (16) the only available synthesis is from 2-methylbutene-3 and hydrogen chloride (15) ; fortunately, the presence of the *iso*-propyl group assists the addition.



$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH . CH{=}CH_2 + HCl \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH . CHClCH_3$$

(15) (16)

The interaction of ethylene and hydrogen chloride has been studied closely and the fact that ethylene in large quantities from ‘ cracker gas ’, together with ‘ synthetic ’ anhydrous hydrogen chloride are both available, has led to their use as a source of ethyl chloride. They are compressed and passed through a catalyst mass, reaction taking place readily.

The conversion of the corresponding alcohol to the chloride is probably the most used method of obtaining the monochloro- derivatives of hydrocarbons. Methyl alcohol and hydrochloric acid readily react under pressure and in the presence of anhydrous zinc chloride to give methyl chloride :—

$$CH_3OH + HCl \longrightarrow CH_3Cl + H_2O$$

and this constitutes the method by which the material is produced industrially.

---

[1] Balz and Schiemann, *Ber.*, 1927, **60**, 1186 ; 1929, **62**, 3035.

The reaction is equally satisfactory for producing ethyl, *n*-propyl, and many higher chlorides, but the ease with which the chloride is formed decreases as the series is ascended and thionyl chloride is a much better reagent, as both by-

$$R\,.\,OH + SOCl_2 \longrightarrow RCl + SO_2 + HCl$$

products are gaseous and leave a crude chloride as the main product. Mention should be made of Marvel's reaction [1] for obtaining the higher members of the normal primary chloroparaffin series. A convenient glycol is selected and allowed to react with *p*-toluene sulphonyl chloride; one hydroxyl is thereby replaced by chlorine and the other esterified by the toluene-*p*-sulphonyl group.

$$\begin{tikzcd}
HO(CH_2)_nOH\,. + CH_3C_6H_4SO_2Cl \arrow[r] & Cl(CH_2)_nO\,.\,SO_2C_6H_4CH_3 \arrow[d, "CH_3(CH_2)_mMgBr"] \\
 & Cl(CH_2)_{n+m}CH_3 + BrMgO\,.\,SO_2C_6H_4CH_3
\end{tikzcd}$$

(17)

If the product so formed reacts with a Grignard reagent the reaction indicated in (17) takes place and a chlorohydrocarbon is produced with a stem which includes both alkyl residues. As ethylene, propylene and butylene glycols are readily available, this method becomes available for the building up of any normal hydrocarbon stem.

This is only one of several methods of employing the Grignard reagent for increasing the length of chain of an alkyl halide. Thus, chloromethyl ether reacts with a Grignard reagent thus :—

$$\begin{tikzcd}
CH_3CH_2CH_2MgBr + ClCH_2OMe \arrow[r] & CH_3CH_2CH_2CH_2OMe \quad (18) \arrow[d] \\
 & CH_3CH_2CH_2CH_2Br \quad (19)
\end{tikzcd}$$

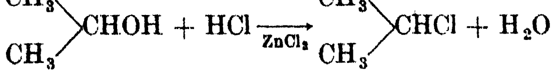
giving, with propylmagnesium bromide, 1-methoxybutane (18) which on heating with concentrated hydrobromic acid, is demethylated and brominated to 1-bromo butane, (19).

Malonic ester synthesis enables the chain to be prolonged by two carbon atoms at a time :—

$$CH_3CH_2CH_2Br + NaCH(COOEt)_2 \longrightarrow CH_3CH_2CH_2CH(COOEt)_2$$
$$\xrightarrow{\text{hydrolysis, etc.}} CH_3CH_2CH_2CH_2COOEt \xrightarrow[\text{alcohol}]{Na} CH_3CH_2CH_2CH_2CH_2OH$$
$$\xrightarrow[HBr]{} CH_3CH_2CH_2CH_2CH_2Br$$

the stages are sufficiently explained by the formulæ above.

Secondary alcohols react quite easily with hydrochloric acid in the presence of zinc chloride and unless complications ensue from intramolecular rearrangement this method constitutes the best method of preparation, e.g. *iso*-propyl chloride is obtained in good yield from *iso*-propyl alcohol and hydrogen chloride :



$$(CH_3)_2CHOH + HCl \xrightarrow[ZnCl_2]{} (CH_3)_2CHCl + H_2O$$

on the other hand, attention has already been drawn (p. 229) to the difficulty of applying this method to other secondary alcohols.

---

[1] **Rossander and Marvel**, *J.A.C.S.*, 1928, **50**, 1491.

TABLE III

Some Aliphatic Chlorine Compounds

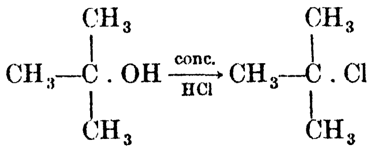
Systematic name	Formula	B.P.	Usual name.
Chloromethane	CH_3Cl	- 23·7° (m. - 103·6°)	Methyl chloride
Chloroethane	C_2H_5Cl	+ 12·2° (m. - 140·8°)	Ethyl chloride
1-Chloropropane	C_3H_7Cl	46·6° (m. - 122·5°)	*n*-Propyl chloride
2-Chloropropane	C_3H_7Cl	36·5°	*iso*-Propyl chloride
1-Chlorobutane	C_4H_9Cl	77·9°	Butyl chloride
2-Chlorobutane	C_4H_9Cl	68·5°	*iso*-Butyl chloride
1-Chloro-2-methylpropane	C_4H_9Cl	66·5°	*sec*-Butyl chloride
2-Chloro-2-methylpropane	C_4H_9Cl	51·5°	*ter*-Butyl chloride
1-Chloropentane	$C_5H_{11}Cl$	106·6°	*n*-Amyl chloride
2-Chloro-2-methylbutane	$C_5H_{11}Cl$	85·0°	*ter*-Amyl chloride
1-Chloro-2,2-dimethyl propane	$C_5H_{11}Cl$	84·4°	*neo*-Pentyl chloride
1-Chlorohexane	$C_6H_{13}Cl$	134°	*n*-Hexyl chloride
1-Chloroheptane	$C_7H_{15}Cl$	159°	*n*-Heptyl chloride
1-Chloroöctane	$C_8H_{17}Cl$	180°	*n*-Octyl chloride
1-Chlorohentriacontane	$C_{31}H_{63}Cl$	— (m. 64·5°)	Myricyl chloride
Dichloromethane	CH_2Cl_2	39·8°	Methylene chloride
1, 1-Dichloroethane	$C_2H_4Cl_2$	58°	Ethylidene chloride
1, 2-Dichloroethane	$C_2H_4Cl_2$	84°	Ethylene chloride
1, 1-Dichloropropane	$CH_3CH_2CHCl_2$	85-87°	
1, 2-Dichloropropane	$C_3H_6Cl_2$	97°	Propylene chloride
2, 2-Dichloropropane	$CH_3CCl_2CH_3$	69·7°	
1, 3-Dichloropropane	$C_3H_6Cl_2$	120°	Trimethylene chloride
1, 4-Dichlorobutane	$C_4H_8Cl_2$	162°	Tetramethylene chloride
1, 5-Dichloropentane	$C_5H_{10}Cl_2$	178°	Pentamethylene chloride
Trichloromethane	$CHCl_3$	61° (m. - 63°)	Chloroform
1,1,1-Trichloroethane	$CH_3 . CCl_3$	74°	Methyl chloroform
1,1,2-Trichloroethane	$CH_2Cl . CHCl_2$	113°	Vinyl trichloride
1, 1, 2-Trichloropropane	$CH_3CHCl . CHCl_2$	140°	
1, 1, 3-Trichloropropane	$CH_2ClCH_2CHCl_2$	146-148°	
1, 2, 3-Trichloropropane	$CH_2Cl . CHCl . CH_2Cl$	158°	Trichlorhydrin
Tetrachloromethane	CCl_4	76·7° (m. - 24°)	Carbon tetrachloride
1, 1, 2, 2-Tetrachloroethane	$CHCl_2 . CHCl_2$	146°	Tetrachlorethane
1, 1, 1, 2-Tetrachloroethane	$CH_2Cl . CCl_3$	130°	—
Pentachloroethane	$CHCl_2 . CCl_3$	162°	—
Hexachloroethane	$CCl_3 . CCl_3$	Melts and sublimes 186°	—
Heptachloropropane	$CHCl_2 . CCl_2 . CCl_3$	248° (m. 30°)	
Octachloropropane	$CCl_3 . CCl_2 . CCl_3$	269° (m. 160°)	
Chloroethylene	$CHCl{=}CH_2$	- 14°	Vinyl chloride
3-Chloropropene-1	$CH_2{=}CH . CH_2Cl$	44°	Allyl chloride
2-Chloropropene-1	$CH_2{=}CCl . CH_3$	23°	β-Chloropropylene
1-Chloropropene-1	$CHCl{=}CH . CH_3$	36°	α-Chloropropylene
1-Chlorobutene-2	$CH_3 . CH{=}CH . CH_2Cl$		Crotyl chloride
3-Chloro-2-methylpropene-1	$CH_2{=}C(CH_3)CH_2Cl$	72°	Methallyl chloride

TABLE III (*continued*)

SOME ALIPHATIC CHLORINE COMPOUNDS

Systematic name	Formula	B.P.	Usual name
1-Chloro-2-methyl-propene-1 . .	$(CH_3)_2 . C=CHCl$.	68°	*iso*-Crotyl chloride
2-Chlorobutadiene-1, 3	$CH_2=CCl . CH=CH_2$		Chloroprene
1, 1-Dichloroethylene	$CH_2=CCl_2$	37°	Acetylidene dichloride
1, 2-Dichloroethylene	$CHCl=CHCl$	(*cis*- 48°) (*trans*- 60°)	Acetylene dichloride
1, 1, 2-Trichloro-ethylene . .	$CHCl=CCl_2$	87°	(Triclene, Westrosol)
Tetrachloroethylene	$CCl_2=CCl_2$	120°	Perchloroethylene
Hexachloropropene	$CCl_2=CCl . CCl_3$	210°	Perchloropropylene
Octachlorobutene-1	$CCl_2=CCl . CCl_2CCl_3$	275°	Perchlorobutylene
Chloroethyne . .	$CH\equiv CCl$	Spontaneously inflammable	Chloroacetylene
Dichloroethyne .	$CCl\equiv CCl$ or $C=CCl_2$	30°	Dichloroacetylene
3-Chloro-propyne-1	$CH\equiv C . CH_2Cl$	65°	Propargyl chloride

Tertiary alcohols react with hydrochloric acid most readily, indeed, the usual method of preparing *tertiary* butyl chloride is to shake the alcohol with concentrated hydrochloric acid in a separating funnel when the reaction



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}} . OH \xrightarrow[HCl]{conc.} CH_3-\underset{CH_3}{\overset{CH_3}{C}} . Cl$$

proceeds almost to completion. The reaction is applicable to most tertiary alcohols.

In cases where rearrangement complicates the conversion of alcohols to their chloro- hydrocarbons, thionyl chloride in the presence of pyridine is often used as a reagent, the pyridine taking up any acid or SO_2 as fast as it is liberated.

In the older literature frequent reference will be found to the use of phosphorus trichloride and pentachloride for the conversion of aliphatic hydroxyl compounds to the chloro- hydrocarbon. This method works fairly well, but has the disadvantage that esters, R_3PO_3, R_3PO_4, are formed at the same time, and that structural changes are easily brought about by the use of such drastic reagents.

The initial members of the series, methyl and ethyl chlorides can be prepared when required in small quantities by the action of dimethyl or diethyl sulphate on a chloride—the most convenient being a saturated solution of calcium chloride in ethanol :—

$$2(CH_3)_2SO_4 + CaCl_2 \longrightarrow 2CH_3Cl + Ca(SO_4)_2(CH_3)_2$$

The systematic and popular names of many of the members of the mono-chlorohydrocarbon series are shown at the beginning of Table III, together with their boiling points.

Invaluable as raw materials for organic syntheses, there are few points of special interest attaching to the individual monochlorohydrocarbons. Methyl chloride has been used widely as a refrigerant and as a methylating agent ; it is toxic, and for this reason has been, to some extent, replaced in refrigeration practice by difluorodichloromethane. Ethyl chloride is valuable as an ethylating agent, and has now almost entirely replaced ethyl bromide as a raw material for the manufacture of lead tetraethyl (*q.v.*). It is used in thermoregulators for ambient heat control, as it boils at 56-58° F., and when confined in an elastic capsule liquefies just below 60° F., causing the capsule to collapse, thus starting up the heating devices. Ethyl chloride has been made recently in U.S.A. by the large-scale addition of hydrogen chloride to ethylene.

POLYCHLORO- HYDROCARBONS

For preparing higher chloro- derivatives an additional method is available, namely, the addition of chlorine to unsaturated hydrocarbons, as in

$$(a)\ CH_2{=}CH_2 + Cl_2 \longrightarrow CH_2Cl\,.\,CH_2Cl$$
$$(b)\ CH{\equiv}CH + 2Cl_2 \longrightarrow CHCl_2\,.\,CHCl_2$$

a method which allows of the formation of di- or tetra- substituted compounds. Tri- and penta- substituted compounds must be obtained by a combined (or sequential) addition of hydrogen chloride and chlorine as in

$$CH{\equiv}CH + HCl \longrightarrow CH_2{=}CHCl + Cl_2 \longrightarrow CH_2Cl\,.\,CHCl_2,$$

or by direct chlorination. Under some conditions, however, the addition of chlorine to acetylene is accompanied by substitution and penta- and hexachloroethanes are obtained :—

$$(a)\ CH{\equiv}CH + 3Cl_2 = CHCl_2\,.\,CCl_3 + HCl$$
$$(b)\ CH{\equiv}CH + 4Cl_2 = CCl_3\,.\,CCl_3 + 2HCl$$

Special methods are used for obtaining the di-, tri- and tetra- chloro substituted methanes which will be referred to specifically below. In occasional instances it is possible to obtain polychloro hydrocarbons by the replacement of oxygen with chlorine ; thus, the persistent action of thionyl chloride on glycerol gives 1, 2, 3-trichloropropane

$$CH_2OH\,.\,CHOH\,.\,CH_2OH \longrightarrow CH_2Cl\,.\,CHCl\,.\,CH_2Cl$$

and aldehydes and ketones react with phosphorus tri- or penta- chloride to give dichloro- compounds in which two chlorine atoms are attached to a single carbon atom as in

$$(a)\ CH_3\,.\,CO\,.\,CH_3 \longrightarrow CH_3CCl_2\,.\,CH_3$$
$$(b)\ CH_3\,.\,CH_2\,.\,CHO \longrightarrow CH_3\,.\,CH_2\,.\,CHCl_2$$

Methylene Chloride.—Discovered by Regnault in 1809,[1] reference has already been made (p. 75) to the preparation of the series methylene chloride, chloroform and carbon tetrachloride by the direct chlorination of methane. The difficulties of separation of the three named constituents can be overcome by the use of suitable plant ; the formation of two- and three-carbon compounds and their complicating influence on the separation has not yet been overcome and the method has not yet been adopted for the preparation of pure compounds.

Methylene chloride is mainly obtained as a by-product in the manufacture of chloroform by reduction of carbon tetrachloride with ' activated ' iron. Carbon tetrachloride, which can be produced very cheaply from carbon disulphide and chlorine, is readily reduced by moist iron which has been ' activated ' by a little hydrochloric acid. Although the main product is chloroform, considerable methylene dichloride is also obtained and is recovered from the fore-run of the distillation. In addition, it is possible to obtain methylene dichloride by the reduction of chloroform with sodium arsenite, but the method has no industrial significance. Reduction of chloroform with the theoretical quantity of alkaline ferrous sulphate is one method which has been adopted on the Continent for methylene chloride production on an industrial scale.

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[1] Regnault, *Ann. Chim. Phys.*, 1809, **71**, 379.

Methylene dichloride is largely replacing ether as a solvent for extraction processes, both in laboratory and industry. Instances are continually being met where the final product must be extracted from an aqueous solution by shaking out with ether ; in nearly all cases ether may, with advantage, be replaced by methylene chloride which boils within a few degrees of ether, is non-inflammable and not only is insoluble in water, but does not dissolve water. Thus, the operation of extraction is made less hazardous ; less costly, since no solvent 'disappears' into the extracted liquid and the final solution on removal of the solvent leaves the product in a reasonably dry condition.

Methylene dichloride is an unreactive body ; Carlisle and Levine[1] have examined its stability, and although it can be made to react with water thus :—

$$CH_2Cl_2 + H_2O \longrightarrow CH_2O + 2HCl$$

very drastic conditions are needed to induce the reaction.

Chloroform.—Liebig[2] and Soubeiran[3] simultaneously reported the preparation of chloroform by the action of alkalies on chloral and by the action of acetone and alcohol on bleaching powder. They regarded it as a chloride of carbon and it remained for Dumas[4] to demonstrate that it contained hydrogen. For the production of chloroform for anæsthetic purposes the action of bleaching powder on alcohol is mainly used in this country. It is a complex reaction in which the alcohol may be considered to be oxidised to aldehyde which is then converted to chloral and hydrolysed :—

$$C_2H_5OH \longrightarrow CH_3CHO \xrightarrow{Cl_2} CCl_3CHO \xrightarrow[H_2O]{} CHCl_3 + H\,.\,COOH$$

In the process used by Poulenc, the efficiency of the older method is increased (for details, see under 'Chloral', Chap. VI) by 'dissecting' the preparation. Aldehyde is made in almost theoretical yield by controlled catalytic vapour-phase oxidation ; vapour-phase chlorination yields chloral in good proportion and hydrolysis with superheated steam not only yields chloroform but enables the formic acid to be retrieved as such. In America much chloroform for industrial purposes is made by the reduction of carbon tetrachloride with moist or 'activated' iron ; but the product so prepared has not been used for anæsthesia. Chloroform for anæsthesia is usually packed with a small percentage of alcohol to remove any phosgene which may be formed by the action of light and moist air :—

$$2CHCl_3 + O_2 \longrightarrow 2COCl_2 + 2HCl$$

The simplest way to purify chloroform for laboratory use is to cool a litre or two in solid CO_2 and acetone, pouring off the supernatant liquid when about two-thirds has crystallised ; on melting the remaining solid chloroform, and repeating the process, a very pure product is obtained. Chloroform melts at − 63°.

Chemically, chloroform is more active than methylene dichloride ; it is readily decomposed by alcoholic potash, giving the formate (*a*) ; with sodium and alcohol ethyl *ortho*-formate is obtained (*b*).

$$CHCl_3 + 4KOH = 3KCl + 2H_2O + HCOOK \quad (a)$$
$$CHCl_3 + 3NaOEt = CH(OEt)_3 + 3NaCl \quad (b)$$

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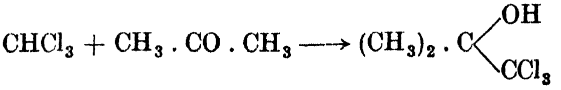
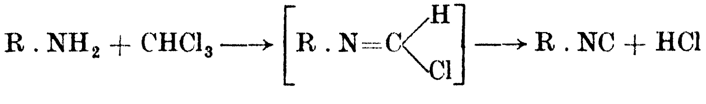
[1] Carlisle and Levine, *Ind. Eng. Chem.*, 1932, **24**, 1164.
[2] Liebig, *Pogg. Ann.*, 1831, **23**, 444.
[3] Soubeiran, *Ann. Chim. Phys.*, 1831, (2), **48**, 131.
[4] Dumas, *Ann.*, 1839, **32**, 113.

Further, the hydrogen atom can enter into an aldol condensation as, for example, with acetone :—



$$CHCl_3 + CH_3 . CO . CH_3 \longrightarrow (CH_3)_2 . C\begin{matrix} \diagup OH \\ \diagdown CCl_3 \end{matrix}$$

The product (1, 1, 1-trichloro-2-methylpropanol-2 or 'chloretone') is used as an antispasmodic. In the presence of alcoholic potash, primary amines react with chloroform to give *iso*cyanides (carbylamines)—notorious for their repulsive odour :—



$$R . NH_2 + CHCl_3 \longrightarrow \left[R . N{=}C\begin{matrix} \diagup H \\ \diagdown Cl \end{matrix}\right] \longrightarrow R . NC + HCl$$

The outstanding property of chloroform is, of course, its power of inducing anæsthesia when its vapour is inhaled. This property, recorded in Edinburgh by Sir J. Simpson[1] in 1848, followed the use of ether in America, and the already widely reported observations of Davy on nitrous oxide anæsthesia. In actual practice, mixtures of chloroform and ether and of ether and nitrous oxide are common. The mechanism of anæsthesia is biochemically obscure; Bancroft[2] has given an interesting explanation based on the fact that chloroform and similar substances will induce coagulation in protein saline systems; the coagulation is reversible, and peptisation can be effected by removing the chloroform. This ability to recover is diminished after some hours when the process becomes irreversible. It is, therefore, held by many that anæsthesia is caused by the anæsthetic dissolving in the lipoid sheath of the nerve, and causing coagulation of the protein saline system within, rendering it temporarily incapable of passing the impulses generated in the sense-perception machinery. The subject is not one which can be discussed in this work at length; the reader is referred, for a general summary of modern views on narcosis and anæsthesia, to the work of H. K. Beecher.[3]

Carbon Tetrachloride—CCl_4, a heavy liquid (d = 1·63), b. 76·7°, is the final product of the chlorination of methane, and was discovered as such by Regnault. It is prepared from methane and chlorine, and from the chlorination of carbon disulphide in the presence of iron powder :—

$$CS_2 + 3Cl_2 \xrightarrow{Fe} CCl_4 + S_2Cl_2$$

The separation of carbon tetrachloride and sulphur monochloride is avoided by cutting off the supply of chlorine when sufficient carbon disulphide still remains to allow the reaction

$$CS_2 + 2S_2Cl_2 \xrightarrow{Fe} CCl_4 + 6S$$

to proceed to completion—which it does readily, leaving a crude carbon tetrachloride to be distilled from the sulphur and rectified.

Carbon tetrachloride is widely used as a solvent, as a remedy for infestation by hookworm, and as a fire extinguisher, being second only to methyl bromide in the latter capacity.

In general, carbon tetrachloride behaves as though one chlorine atom is linked differently; no *ortho*-carbonic esters are produced by hydrolysis in presence of sodium ethylate; ethyl *ortho*formate can be isolated, and it is presumed that a reaction proceeds with the formation of chloroform which then gives rise to the *ortho*formate. Again, carbon tetrachloride reacts readily with silver perchlorate[1] to give trichloromethyl perchlorate, a reactive liquid

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[1] Simpson, *Edin. Monthly Journal of Med. Sci.*, 1848, **8**, 415.

[2] Bancroft and Richter, *J. Physiol. Chem.*, 1931, **35**, 215.

[3] Beecher, *The Physiology of Anæsthesia*, pp. 1-54, 1938, O.U. Press.

$$CCl_4 + AgClO_4 \longrightarrow CCl_3(ClO_4) + AgCl$$

instantly decomposed by water to form perchloric acid and CCl_3OH. The general behaviour is compatible with a tendency towards the formation of a structure

$$CCl_4 \rightleftharpoons [CCl_3]Cl$$

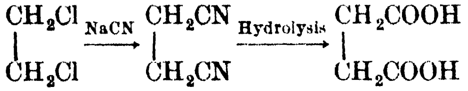
The reduction of carbon tetrachloride to chloroform and methylene dichloride has already been mentioned. Carbon tetrachloride gives some carbylamine when heated with a primary amine and alcoholic potash.

1, 2-Dichlorethane (*Ethylene dichloride*).[2]—In 1795, Bondt, Deimann, Louwenburgh and van Troostwick discovered ethylene dichloride by the union of ethylene and chlorine; for obvious reasons it received the name "Oil of the Dutch chemists". It is almost universally prepared by the direct action of chlorine upon ethylene, and considerable ingenuity has been directed towards obtaining a pure product. The use of crude ethylene (e.g. from the partial liquefaction of coke-oven gas) is liable to give a chlorinated product containing other halogen derivatives beside ethylene dichloride, and it is preferable to fractionate the ethylene to obtain a tolerably pure gas before chlorination. The most satisfactory condition for the production of high grade ethylene dichloride is the passage of dry ethylene into liquid chlorine[3]; higher temperatures lead to some substitution, as well as addition.

Ethylene dichloride is a stable substance; its main use in the manufacture of 'Thiokol' elastomers has already been discussed, as also has its progressive conversion to acetylene by alcoholic alkali :—

$$CH_2Cl\,.\,CH_2Cl \xrightarrow{KOH} CHCl{=}CH_2 \xrightarrow{KOH} CH{\equiv}CH$$

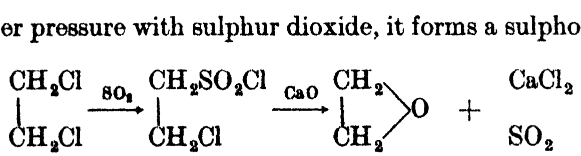
It can be made to react with dilute aqueous alkalies to give ethylene glycol, and its interaction with sodium cyanide gives the nitrile of succinic acid, from which the industrial supplies of that acid are obtained.



$$\begin{array}{c}CH_2Cl\\|\\CH_2Cl\end{array}\xrightarrow{NaCN}\begin{array}{c}CH_2CN\\|\\CH_2CN\end{array}\xrightarrow{\text{Hydrolysis}}\begin{array}{c}CH_2COOH\\|\\CH_2COOH\end{array}$$

Heating ethylene dichloride under pressure with alkalies of a suitable concentration in the presence of sodium acetate can give a mixture of vinyl chloride and acetate.

Heated under pressure with sulphur dioxide, it forms a sulphonyl chloride :—



$$\begin{array}{c}CH_2Cl\\|\\CH_2Cl\end{array}\xrightarrow{SO_2}\begin{array}{c}CH_2SO_2Cl\\|\\CH_2Cl\end{array}\xrightarrow{CaO}\begin{array}{c}CH_2\\|\\CH_2\end{array}\!\!>O \;+\; \begin{array}{c}CaCl_2\\SO_2\end{array}$$

This substance, 2-chloroethanesulphonyl chloride decomposes readily with lime to give ethylene oxide.

The reaction between ethylene dichloride and ammonia is of considerable industrial importance, and constitutes Kraut's method[4] of making ethylene diamine. The dichloride is heated with ammonia under pressure when the reaction proceeds :—

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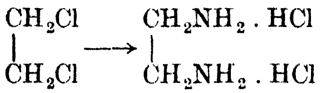
[1] Birckenbach and Goubeau, *Naturwiss.*, 1930, **18**, 530.

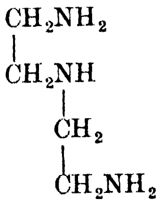
[2] Bibliography of Ethylene Dichloride, U.S. Dept. of Agriculture, 1932, Miscellaneous Publication, No. 117.

[3] Curme, *Chem. Met. Eng.*, 1921, **25**, 999.

[4] Kraut, *Ann.*, 1882, **212**, 253.

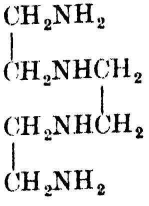


$$\begin{array}{l} CH_2Cl \\ | \\ CH_2Cl \end{array} \longrightarrow \begin{array}{l} CH_2NH_2 \,.\, HCl \\ | \\ CH_2NH_2 \,.\, HCl \end{array}$$



$$\begin{array}{l} CH_2NH_2 \\ | \\ CH_2NH \\ \quad | \\ \quad CH_2 \\ \quad | \\ \quad CH_2NH_2 \end{array}$$

(20)



$$\begin{array}{l} CH_2NH_2 \\ | \\ CH_2NHCH_2 \\ \qquad\qquad | \\ CH_2NHCH_2 \\ | \\ CH_2NH_2 \end{array}$$

(21)

In addition the secondary amines (20) and (21), *bis*(2-aminoethyl)amine and *bis*(2-aminoethyl)ethylenediamine, are formed to a limited extent.[1]

Ethylidene chloride, CH_3CHCl_2, a substance less well known than its isomer, ethylene dichloride, is prepared in laboratory quantities by the action of phosphorus pentachloride on acetaldehyde. The yield is poor, and may be improved on a somewhat larger scale by autoclaving acetaldehyde and phosgene, the reaction

$$CH_3CHO + COCl_2 \longrightarrow CH_3CHCl_2 + CO_2$$

proceeding easily and with little secondary decomposition. If required on an industrial scale, it could be prepared by passing the vapour of ethylene dichloride over alumina at 400°, when it is split to vinyl chloride and hydrogen chloride, recombination by passage through aluminium chloride at 125° gives ethylidene chloride :—

$$CH_2Cl \,.\, CH_2Cl \xrightarrow[400^\circ]{Al_2O_3} CHCl{=}CH_2 + HCl \xrightarrow[125^\circ]{AlCl_3} CHCl_2 \,.\, CH_3$$

Hydrolysis of ethylidene chloride yields acetaldehyde.

There are three trichloro- derivatives of interest in this field, namely, methylchloroform, 1, 1, 2-trichloroethane and 1, 2, 3-trichloropropane. Methylchloroform, CH_3CCl_3, is best made by chlorinating ethylidene chloride, although it can be prepared by the prolonged action of phosphorus pentachloride on acetyl chloride. Its isomer, 1, 1, 2-trichloroethane, is obtained by the regulated action of chlorine on ethylene dichloride.

1, 2, 3-Trichloropropane is easily obtained from glycerol and thionyl chloride or phosphorus pentachloride ; it is a heavy liquid, b. 158°, with a pleasant smell.

Tetrachloroethane, $CHCl_2 \,.\, CHCl_2$, a heavy, sweet-smelling liquid, highly toxic and a cumulative poison, is obtained by passing acetylene and chlorine into antimony pentachloride in tetrachloroethane solution. It is very reactive and in the presence of moisture rapidly corrodes iron, zinc, and similar metals. It is readily decomposed by alkalies yielding trichloroethylene, and with air and steam yields dichloroacetic acid :—

$$CHCl_2 \,.\, CHCl_2 \xrightarrow[H_2O]{O_2} CHCl_2 \,.\, COOH$$

It is one of the most powerful solvents known, and but for its toxicity hazard would be used more widely in industry.

Penta- and hexachloroethane, $CHCl_2 \,.\, CCl_3$ and $CCl_3 \,.\, CCl_3$. These substances are produced as by-products in the preparation of tetrachloroethane, from which they may be separated by fractional distillation. The main use of pentachloroethane is as a high-boiling solvent ; the entrance of the sixth chlorine atom induces a striking change in physical properties ; hexachloroethane is a crystalline solid, m.p. 186°, with a strong camphor-like odour. It is used in compounding smoke-screens—mixtures of zinc dust and hexachloroethane; it also finds use as a plasticiser.

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[1] Fargher, *J.C.S.*, 1920, **117**, 1351.

Few of the higher chlorinated propanes or butanes are of exceptional interest; their physical properties are detailed in Table III; 1, 3-dichloropropane is a valuable starting point for the anæsthetic cyclopropane, but few of the others have found application.

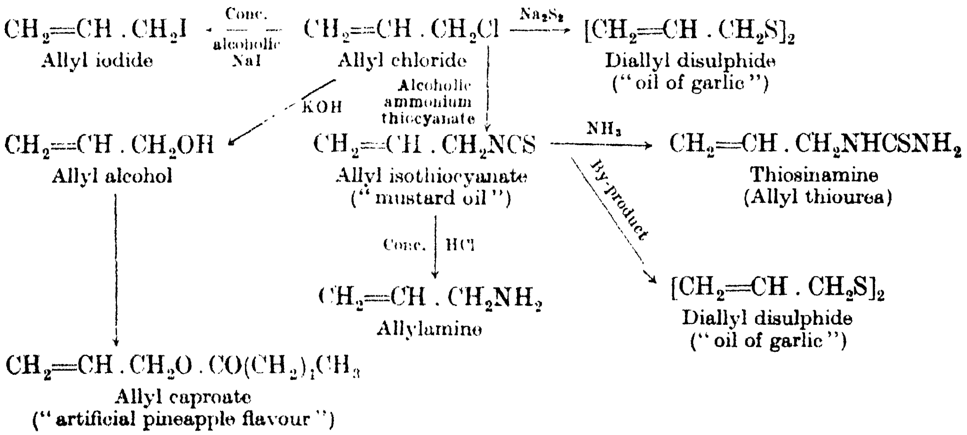
UNSATURATED CHLOROHYDROCARBONS

The simplest of these, vinyl chloride, $CH_2{=}CHCl$, is a gas at ordinary temperatures, b. − 14°. It has a powerful odour, and whilst it can be prepared by the controlled reaction of alkalies on ethylene dichloride, it is nearly all manufactured by the direct union of acetylene and hydrogen chloride in the presence of cuprous chloride :—

$$CH{\equiv}CH + HCl \longrightarrow CH_2{=}CHCl$$

The polymerisation of vinyl chloride has been described in Appendix I., Chapter III.

The polymeric tendency is found also in allyl chloride, $CH_2{=}CH\,.\,CH_2Cl$, obtained as an intermediate product in the manufacture of glycerol from propylene. It is sold in large tonnage in America, and is the source of nearly all the allyl compounds of commerce. The formation of some of these is shown below :—



Although allyl chloride does not polymerise so readily as vinyl chloride, the tendency is still present, and Staudinger and co-workers[1] showed that a linear polymer

$$\ldots\ CH_2\,.\,CH(CH_2Cl)[CH_2\,.\,CH(CH_2Cl)]_nCH_2CH(CH_2Cl)\ \ldots$$

was obtained on prolonged standing; polymers with 5, 7, 9, 11, 12 and 25 units were isolated. Analogous substances were obtained from 1, 1-dichloroethylene.[2]

Methallyl chloride, $CH_2{=}C(CH_3)CH_2Cl$, is obtained in industrial quantities by the direct chlorination of *iso*-butene :—

$$CH_2{=}C(CH_3)_2 + Cl_2 \longrightarrow CH_2{=}C(CH_3)CH_2Cl + HCl$$

[1] Staudinger and Fleitmann, *Ann.*, 1930, **480**, 92.

[2] Staudinger *et al.*, *Helv. Chim. Acta*, 1930, **13**, 805 and 832.

and undergoes a series of reactions similar to those described in the case of allyl chloride. It is an interesting fact that the chlorination of *iso*-butene leads largely to a substitution product, and that addition is almost undetectable; this is probably related to the well-known stability of the *neo*-pentyl compounds. The term ‘ allyl rearrangement ’ has been given to the shift of double bond which is encountered in this group; thus, if methyl vinyl carbinol is treated with a halogen acid a reaction takes place :—

$$CH_3CH(OH)CH{=}CH_2 \underset{AgOH}{\overset{HCl}{\rightleftarrows}} CH_3CH{=}CH\ .\ CH_2Cl$$

On the other hand, when the halide is treated with silver hydroxide the original alcohol is reconstituted and the shift takes place in the opposite direction. The reaction is a general one, and an interesting example is that observed by Prévost,[1] the abnormal reaction of the Grignard reagent with crotyl bromide

$$CH_3CH{=}CH\ .\ CH_2Br + CH_3MgBr \longrightarrow (CH_3)_2CH\ .\ CH{=}CH_2$$

2-Chlorobutadiene-1, 3 (Chloroprene).—Reference has already been made (Appendix 1, Chap. III) to the place which this substance holds in the manufacture of ‘ Neoprene ’. Its usual method of preparation is by the action of acetylene on hydrogen chloride in the presence of catalysts :—

$$CH{\equiv}CH + CH{\equiv}CH \longrightarrow CH{\equiv}C\ .\ CH{=}CH_2 + HCl \longrightarrow \underset{\text{Chloroprene}}{CH_2{=}CCl\ .\ CH\quad CH_2}$$

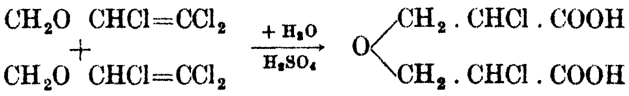
Apart from its rapid polymerisation to ‘ Neoprene ’, little application of this compound has been developed.

Trichloroethylene, $CHCl{=}CCl_2$.—This substance is readily obtained from tetrachloroethane by the action of alkalies, and is probably the most widely used solvent of the series. It is preferable to tetrachloroethane for many purposes, as it does not so readily cause corrosion, and, in general, its chlorine atoms are inert. Pure trichloroethylene is an excellent anæsthetic, and offers certain advantages over chloroform; it is manufactured industrially for this purpose. It is also used in large quantities in mechanical degreasing plants and for fat extraction from press-cakes in the vegetable oil industry.

Chemically, trichloroethylene is a valuable source of chloroacetic acid, since when heated with dilute hydrochloric acid under pressure the following reaction takes place almost quantitatively.

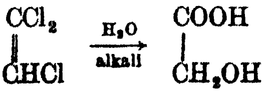
$$ClCH{=}CCl_2 \xrightarrow[-\,HCl]{+\,H_2O} CH_2Cl\ .\ COCl \xrightarrow[-\,HCl]{+\,H_2O} CH_2Cl\ .\ COOH$$

It is also the most convenient source of dichlorodinitromethane, $Cl_2C(NO_2)_2$, which is obtained by the action of nitric acid; whilst with formaldehyde and sulphuric acid it gives an ether, thus :—



$$\begin{array}{l} CH_2O\ \ CHCl{=}CCl_2 \\ \quad + \\ CH_2O\ \ CHCl{=}CCl_2 \end{array} \xrightarrow[H_2SO_4]{+\,H_2O} O\begin{cases} CH_2\ .\ CHCl\ .\ COOH \\ CH_2\ .\ CHCl\ .\ COOH \end{cases}$$

In alkaline solution, trichloroethylene is hydrolysed to glycollic acid—a method which is used for obtaining that acid for experimental purposes :—

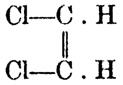


$$\begin{array}{c} CCl_2 \\ \| \\ CHCl \end{array} \xrightarrow[\text{alkali}]{H_2O} \begin{array}{c} COOH \\ | \\ CH_2OH \end{array}$$

---

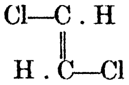
[1] Prévost, *Ann. Chim.*, 1928 (10), **10**, 121; Prévost and Danjat, *Bull. Soc. Chim.*, 1930, **47**, 588.

When tetrachloroethane is reduced with moist iron, dichloroethylene, $CHCl{=}CHCl$, is obtained. The industrial solvent used under this name is a mixture of the *cis-* and *trans-* forms which can be separated by careful fractionation. They are probably the simplest compounds showing geometrical isomerism.



$$\begin{array}{l} Cl—C\,.\,H \\ \quad\ \ \| \\ Cl—C\,.\,H \end{array}$$

cis-dichloroethylene
b. 48°

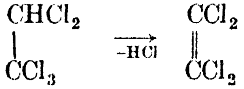


$$\begin{array}{l} Cl—C\,.\,H \\ \qquad\ \ \| \\ H\,.\,C—Cl \end{array}$$

trans-dichloroethylene
b. 60°

Like methylene dichloride, dichloroethylene can be used to replace ether in a large variety of laboratory extractions.

Tetrachloroethylene, $CCl_2{=}CCl_2$.—This substance is prepared from pentachloroethane by a process analogous to the formation of trichloroethylene from tetrachloroethane, namely, the elimination of hydrogen chloride :—



$$\begin{array}{l} CHCl_2 \\ | \\ CCl_3 \end{array} \xrightarrow[-HCl]{} \begin{array}{l} CCl_2 \\ \| \\ CCl_2 \end{array}$$

It offers one advantage over the other non-corrosive chlorinated solvents namely, a boiling point of 120°, which is an advantage in certain extractions The chlorine atoms are not easily reactive. It is used in textile soaps, and as a remedy for liver-fluke in sheep.

There are only two chloro- derivatives of acetylene possible, namely, $ClC{\equiv}CH$ and $ClC{\equiv}CCl$. Both have been prepared by passing the vapours of di- or tri-chloroethylene over heated solid potash (120-150°). They are spontaneously inflammable or explosive substances of considerable toxicity and powerful odour. These abnormal properties led Nef to propose a divalent carbon structure, e.g., $C{=}CCl_2$, for them, but no critical experiments have been recorded leading to a verification of this hypothesis.

On the other hand, the allylene chlorides are normal substances, such, for example, as allylene chloride itself (better known as 1-chloropropyne-1), $CH_3C{\equiv}C\,.\,Cl$, prepared by the action of allylene on sodium hypochlorite. The isomeric 1-chloropropyne-3 ($CH{\equiv}C\,.\,CH_2Cl$) is obtained from propargyl alcohol.

BROMINE COMPOUNDS

A list of the names and properties of the more prominent bromine derivatives is given in Table IV on page 244.

The direct bromination of hydrocarbons seldom produces compounds with more than one bromine atom per carbon, hence compounds with more than this amount of bromine must be obtained by indirect methods, such as the addition of bromine, or the replacement of aldehyde or keto-oxygen by treatment with phosphorus pentabromide. On the other hand, there are one or two satisfactory methods available for the preparation of the bromides which do not work well in the case of the corresponding chlorides. Thus, in proceeding from one halide to the next highest the Grignard reagent may be used thus :—

$$C_3H_7Br \xrightarrow{Mg} C_3H_7MgBr \xrightarrow{CH_2O} C_3H_7CH_2OH \xrightarrow[HBr]{} C_3H_7CH_2Br$$

a variant method is to react the Grignard compound with monochloromethyl ether :—

$$C_3H_7MgBr + ClCH_2\,.\,OCH_3 \longrightarrow C_3H_7CH_2OCH_3 \xrightarrow[HBr]{} C_3H_7\,.\,CH_2Br$$

TABLE IV

Systematic name	Formula	B.P.	Usual name
Bromomethane	CH_3Br	4·6°	Methyl bromide
Bromoethane	C_2H_5Br	38·4°	Ethyl bromide
1-Bromopropane	$CH_2Br\,.\,CH_2CH_3$	70·9°	*n*-Propyl bromide
2-Bromopropane	$CH_3CHBr\,.\,CH_3$	59·6°	*iso*-Propyl bromide
1-Bromobutane	$CH_2Br(CH_2)_2CH_3$	101·6°	*n*-Butyl bromide
2-Bromobutane	$CH_3\,.\,CH_2BrCH_2CH_3$	91°	*sec*-Butyl bromide
1-Bromo-2-methylpropane	$CH_2Br\,.\,CH(CH_3)CH_3$	92°	*iso*-Butyl bromide
2-Bromo-2-methylpropane	$(CH_3)_3CBr$	72°	*ter*-Butyl bromide
1-Bromopentane	$CH_2Br(CH_2)_3CH_3$	128°	*n*-Amyl bromide
2-Bromo-2-methylbutane	$CH_3CBr(CH_3)CH_2CH_3$	108°	*ter*-Amyl bromide
1-Bromo-2, 2-dimethylpropane	$(CH_3)_3C\,.\,CH_2Br$	105°	*neo*-Pentyl bromide
1-Bromohexane	$CH_2Br(CH_2)_4CH_3$	156°	Hexyl bromide
1-Bromoheptane	$CH_2Br(CH_2)_5CH_3$	178°	Heptyl bromide
1-Bromooctane	$CH_2Br(CH_2)_6CH_3$	202°	Octyl bromide
1-Bromohexadecane	$CH_2Br(CH_2)_{14}CH_3$	— m. 15°	Cetyl bromide
1-Bromohentriacontane	$CH_2Br(CH_2)_{29}CH_3$	— m. 67°	Myricyl bromide
Dibromomethane	CH_2Br_2	90°	Methylene dibromide
1, 1-Dibromoethane	$CHBr_2\,.\,CH_3$	110°	Ethylidene dibromide
1, 2-Dibromoethane	$CH_2Br\,.\,CH_2Br$	131°, m. 9°	Ethylene dibromide
1, 2-Dibromopropane	$CH_3CHBrCH_2Br$	142°	Propylene dibromide
1, 3-Dibromopropane	$CH_2BrCH_2CH_2Br$	167°	Trimethylene dibromide
1, 4-Dibromobutane	$CH_2Br(CH_2)_2CH_2Br$	197°	Tetramethylene dibromide
1, 5-Dibromopentane	$CH_2Br(CH_2)_3CH_2Br$	223°	Pentamethylene dibromide
Tribromomethane	$CHBr_3$	151°, m. 7·7°	Bromoform
1, 2, 3-Tribromopropane	$CH_2Br\,.\,CHBr\,.\,CH_2Br$	220°	Glyceryl bromide
Tetrabromoethane	CBr_4	189°, m. 94°	Carbon tetrabromide
Bromoethylene	$CH_2{=}CHBr$	16°	Vinyl bromide
1-Bromopropene-2	$CH_2Br\,.\,CH{=}CH_2$	71°	Allyl bromide
Bromoethyne	$CH{\equiv}CBr$	-2°	Bromoacetylene
Dibromoethyne	$CBr{\equiv}CBr$	77°	Dibromoacetylene

The ether which is obtained in this way can be converted by boiling hydrobromic acid to the alkyl bromide.

The synthesis of Marvel is available for preparing tetra-, penta- and hexamethylene dibromides. Thus, trimethylene dibromide (22) is treated with sodium phenoxide when the mono-phenoxy compound (23) is formed. This is transformed by the series of orthodox changes outlined below to tetramethylene dibromide.

$$\begin{array}{rll} & Br\,.\,CH_2CH_2CH_2Br & (22) \\ \text{PhONa}\downarrow & PhO\,.\,CH_2CH_2CH_2Br & (23) \\ & PhO\,.\,CH_2CH_2CH_2CN & \downarrow \text{KCN} \\ & PhO\,.\,CH_2CH_2CH_2COOEt & \text{H}_2\text{SO}_4/\text{EtOH} \\ & PhO\,.\,CH_2CH_2CH_2CH_2OH & \text{Na/EtOH} \\ & Br\,.\,CH_2CH_2CH_2CH_2Br & \text{HBr} \end{array}$$

In general, it may be added that the simple alkyl bromides are the compounds of this series most commonly met with.

Methyl and ethyl bromides are useful methylating and ethylating agents for laboratory use, but find little industrial application in this capacity. The main use of methyl bromide is in fire-extinguishing plant ; the release of methyl bromide in and around a fire area blankets the fire, and about 10-12 per cent. of methyl bromide in an atmosphere makes it virtually a non-supporter of combustion.

Bromoform, on account of its therapeutic use, is an article of commerce; it is a very heavy liquid (d. 2·9) obtained by the action of sodium hypobromite on acetone. When bromoform is allowed to stand with excess of sodium hypobromite, carbon tetrabromide is formed as a crystalline solid, m. 94°. Warming with alkalies readily converts carbon tetrabromide back to bromoform, the reaction being reversible

$$CBr_4 + KOH \rightleftharpoons CHBr_3 + KOBr$$

It appears that the 'positive' nature of one of the chlorine atoms in carbon tetrachloride is enhanced in the corresponding bromine atom of carbon tetrabromide which might, therefore, be written $[CBr_3]Br$.

The most important bromine compound in this series, from an industrial standpoint, is ethylene dibromide, $CH_2Br . CH_2Br$, which is used with lead tetraethyl in the production of anti-knock fuel. Without the bromide some metallic lead is produced which is only partially converted to the oxide; the metallic material is deposited on, and interferes with, the ignition points. The use of ethylene dibromide leads to the formation of lead bromide which is harmless. It may be added that the chloride is not suitable—as lead chloride is not formed under the conditions existing in the cylinder. Many tons of bromine are needed for this material—U.S.A. used over 6000 tons of ethylene dibromide in 1936—and it was in connexion with this chemical that the process of obtaining bromine from sea-water was industrially developed. It is now combined with the extraction of magnesium from the same source. The advent of simple processes for catalytic products of very high octane value fuels has to some degree lessened the need for 'leading' petrol; it may be that these will, in future, replace the leaded fuel.

IODINE COMPOUNDS

Iodine compounds are produced less easily, in general, than the corresponding bromine derivatives. The direct introduction of iodine is exceptional, so that iodo-compounds are mainly obtained by the replacement of the hydroxyl of alcohols by iodine, using hydriodic acid (or its equivalent, phosphorus, iodine and water) or by the addition of hydriodic acid to unsaturated compounds. As with the bromides, iodomethane and iodoethane (methyl and ethyl iodide) can be obtained by the action of dimethyl or diethyl sulphate on potassium iodide:—

$$\begin{array}{ll} (CH_3)_2SO_4 + KI \longrightarrow & K(CH_3)SO_4 + CH_3I \\ & \quad \Big\downarrow {\scriptstyle KI} \\ & K_2SO_4 + CH_3I \end{array}$$

Some important aliphatic iodine compounds are set out in Table V on page 246.

SOME REACTIONS OF ALKYL HALIDES

The great ease with which the reactions

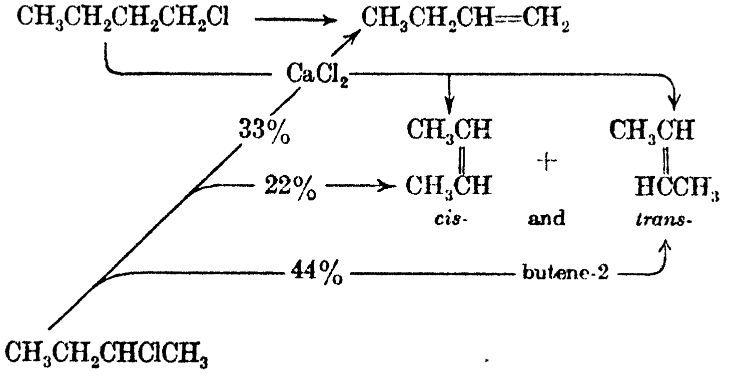
$$R . Br + KI \longrightarrow RI + KBr$$
$$R . Cl + KI \longrightarrow RI + KCl$$

proceed affords a simple method of making the alkyl iodides from the bromides or chlorides. The lability of the iodine in iodides makes them extremely reactive, and the ease with which they enter into reaction with sodio- derivatives of malonic ester, or form Grignard compounds, is contrasted with the difficulty of inducing corresponding reactions with the chloro- compounds. This lability is one factor in the difficulty of preparing iodine derivatives of certain branched chain hydrocarbons, since iodine is readily transferred from one carbon atom to another, e.g., when *n*-propyl iodide is refluxed for a few hours it is converted to *iso*-propyl iodide, and the reaction is even more readily induced by heating under pressure. The reaction is not unknown with bromo- and chloro-compounds, but is not always so readily induced with primary halides; however, *sec*-butyl bromide is readily converted to *ter*-butyl bromide by heating [1] under pressure to 230°, an equilibrium being attained when 80-85 per cent. conversion to the *ter*- form has been formed, and the reader will recall, in this connexion, the many examples of radicle isomerisation observed during the Friedel-Crafts reaction between alkyl halides and aromatic hydrocarbons.

TABLE V

SOME IODINE COMPOUNDS

Systematic name	Formula	B. P.	Usual name
Iodomethane	CH_3I	42·6°	Methyl iodide
Iodoethane	CH_3CH_2I	72°	Ethyl iodide
1-Iodopropane	$CH_3CH_2CH_2I$	102·5°	*n*-Propyl iodide
2-Iodopropane	CH_3CHICH_3	89·5°	*iso*-Propyl iodide
1-Iodobutane	$CH_3(CH_2)_2CH_2I$	127°	*n*-Butyl iodide
2-Iodobutane	$CH_3CH_2CHICH_3$	120°	*sec*-Butyl iodide
1-Iodo-2-methylpropane	$CH_3CH(CH_3)CH_2I$	119°	*iso*-Butyl iodide
2-Iodo-2-methylpropane	$(CH_3)_3CI$	100°	*ter*-Butyl iodide
1-Iodopentane	$CH_3(CH_2)_3CH_2I$	156°	*n*-Amyl iodide
2-Iodo-2-methylbutane	$CH_3 . CH_2 . C(CH_3)_2I$	127°	*ter*-Amyl iodide
1-Iodo-2, 2-dimethylpropane	$(CH_3)_3C . CH_2I$	133°	Neopentyl iodide
1-Iodohexane	$CH_3(CH_2)_5I$	177°	Hexyl iodide
1-Iodoheptane	$CH_3(CH_2)_6I$	204°	Heptyl iodide
1-Iodo-octane	$CH_3(CH_2)_7I$	221°	Octyl iodide
2-Iodo-octane	$CH_3(CH_2)_6CHICH_3$	210°	*sec*-Octyl iodide
1-Iodohexadecane	$CH_3(CH_2)_{15}I$	211°/15 mm. m. 22°	Cetyl iodide
1-Iodohentriacontane	$CH_3(CH_2)_{30}I$	— m. 70°	Myricyl iodide
Di-iodomethane	CH_2I_2	181°, m. 5·5–8°	Methylene iodide
1, 2-Di-iodoethane	$CH_2I . CH_2I$	— m. 81°	Ethylene iodide
Tri-iodomethane	CHI_3	— m. 120°	Iodoform
1-Iodopropene-2	$CH_2{=}CHCH_2I$	103°	Allyl iodide



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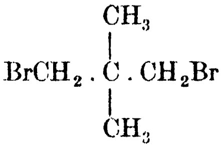
[1] Michael *et al.*, *Ann.*, 1912, **393**, 81; *J.A.C.S.*, 1916, **38**, 653; Brunel, *ibid.*, 1917, **39**, 1978.

It may also be added that owing to the lability of the halogen atom it is difficult to forecast the course of any reaction in which an alkyl halide is involved; thus, if 1-chlorobutane is passed through a heated tube, the expected decomposition to butene-1 and hydrogen chloride takes place; on the other hand, if the tube is packed with calcium chloride *cis*- and *trans*-butene are the products; further, as might be anticipated, 2-chlorobutane yields a mixture of butene-1, *cis*- and *trans*-butene-2 when heated alone; with calcium chloride the amount of butene-1 is halved, and the yield of butene-2 correspondingly increased. (See scheme at foot of p. 246.)

Several examples from the alkylene dibromide series show that the lability of the halogen is to a large extent governed by the nature of the groups attached to the carbon atom adjacent to that which carries the halogen. Thus, trimethylene dibromide (24) (1, 3-dibromopropane) reacts easily both with sodium cyanide to form a dinitrile, and with aqueous sodium carbonate to form a glycol; neither the dimethyl- nor the methyl-ethyl-derivatives (25) and (26) react at all readily with either reagent; the methyl-ethyl derivative is quite unchanged by 33 hours' boiling with aqueous sodium carbonate, although the phenyl-methyl derivative (27) is converted to the glycol completely after 12 hours' boiling.

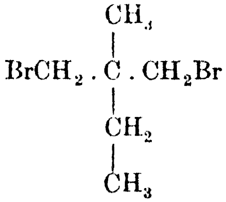
$BrCH_2 . CH_2 . CH_2Br$

(24)



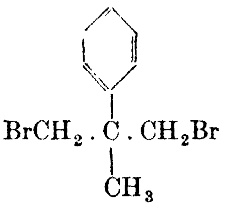
$$\begin{array}{c} CH_3 \\ | \\ BrCH_2 . C . CH_2Br \\ | \\ CH_3 \end{array}$$

(25)



$$\begin{array}{c} CH_3 \\ | \\ BrCH_2 . C . CH_2Br \\ | \\ CH_2 \\ | \\ CH_3 \end{array}$$

(26)



(27)

Many experiments have been made to measure the lability of the halogens in a homologous series of aliphatic halides. The figures obtained by Segaller[1] are illustrated in the curve below. The smooth curve represents the rate of reaction of the *n*-alkyl bromides with sodium phenoxide in alcoholic solution. Similar figures were obtained by Haywood[2] in corresponding reactions with sodium benzyl oxide, $C_6H_5 . CH_2ONa$. In each case halides with *iso*- stems have an abnormally low reaction velocity (shown in Fig. IV, by 'X' for *iso*-butyl and *iso*-amyl).

The sluggishness of the reacting halogen in *iso*- and *secondary*-halides is very well shown in the results of McElvain and Selb's[3] experiments on the interaction of halides with piperidine at 90°; the results are shown graphically in Fig. IV, the extreme activating influence of the aryl group will be noted from the values given for benzyl and phenyl ethyl bromides.

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[1] Segaller, *J.C.S.*, 1914, **105**, 106.

[2] Haywood, *ibid.*, 1922, **121**, 1904.

[3] McElvain and Selb, *J.A.C.S.*, 1931, **53**, 690.

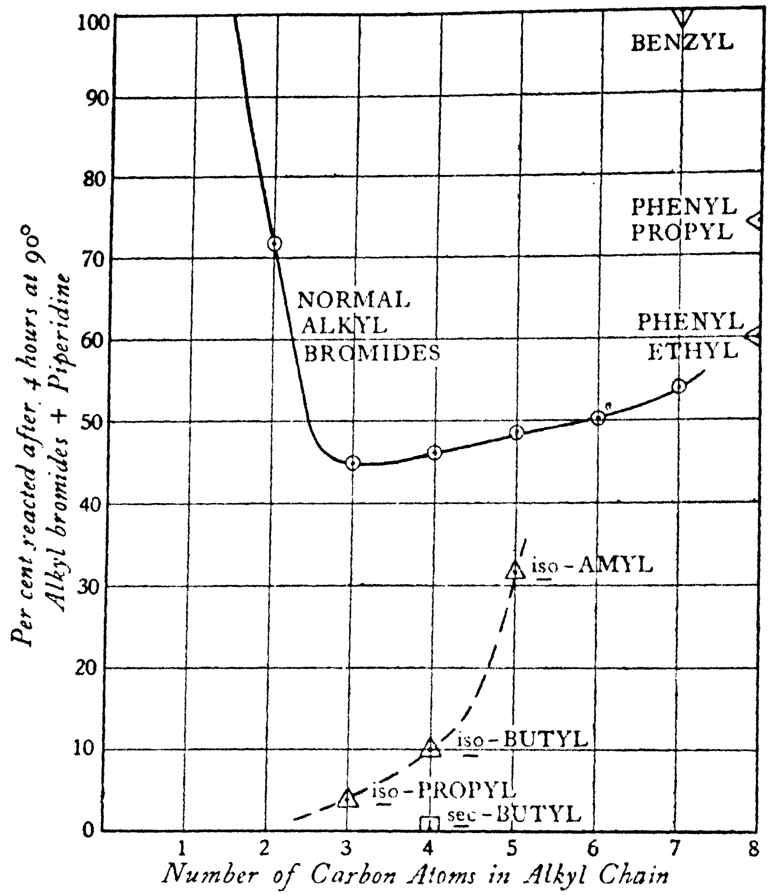
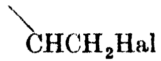


FIG. IV.—Carbon atoms in alkyl chain.

It is sometimes convenient to classify the halides in the groups below :—

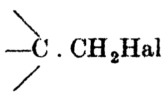
Group I ——— Hal

Group II



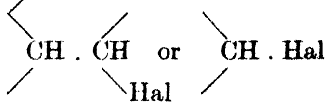
$>CHCH_2Hal$

Group III



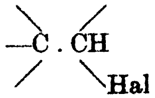
$-C{<}.CH_2Hal$

Group IV



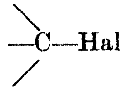
$>CH.CH{<}_{Hal}$ or $>CH.Hal$

Group V



$-C{<}.CH{<}_{Hal}$

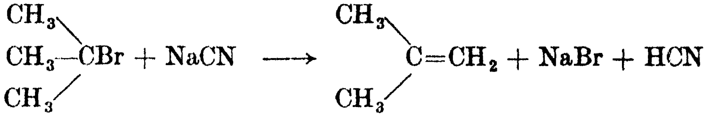
Group VI



$-C{<}-Hal$

in each case the line " —— " indicates a normal chain of one or more carbon atoms ; Groups I, II and III are primary halides ; Groups IV and V are secondary, and Group VI tertiary.

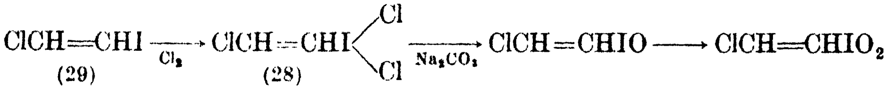
Reactions involving the exchange of halogen for another group such as —OH, OAlk, —CN or with sodio- derivatives such as sodiomalonic ester, are only easily accomplished with Group I ; Groups II and III react with difficulty and with Groups IV, V and VI the tendency is to form an olefine and the acid e.g.,



$$(CH_3)_3CBr + NaCN \longrightarrow (CH_3)_2C{=}CH_2 + NaBr + HCN$$

with correspondingly poor yields of the desired compounds.

The tendency of iodine to form trivalent compounds, so characteristic of the aryl iodides (see p. 255) is but poorly developed in the aliphatic series; indeed, it appears that for stability the $-\overset{\diagdown}{\underset{\diagup}{C}}-I$ group must be backed by unsaturation. Thiele[1] investigated the aliphatic trivalent iodine compounds and found the chloro-iodo-ethylenes, e.g. (29), to be the only types capable of forming stable compounds at ordinary temperatures. Thus, chloro-iodo-ethylene (29) forms the iodo-dichloride, the iodoso- and iodoxy- compounds :—



$$\underset{(29)}{ClCH{=}CHI} \xrightarrow[Cl_2]{} \underset{(28)}{ClCH{=}CHICl_2} \xrightarrow[Na_2CO_3]{} ClCH{=}CHIO \longrightarrow ClCH{=}CHIO_2$$

Reference has already been made to the conversion of halides by reducing agents to hydrocarbons (Chap. III); some of the more usual methods are summarised below.

(1) *Zinc-copper-couple.*—The use of this reagent (often called by the names of its originators, Gladstone and Tribe[2]), is successful with iodides, and is best accomplished by adding the iodide to an alcoholic suspension of the couple; the reaction proceeds

$$C_2H_5I + H_2 \longrightarrow C_2H_6 + HI$$

Various modifications of this reagent have been devised; Zelinski[3] used a zinc/palladium couple in the presence of dilute hydrochloric acid, and Clarke[4] dispensed with the couple and used zinc and hydrochloric acid. The application of the reaction to dibromides was shown by Linnemann[5] who obtained pure propylene from propylene dibromide, zinc turnings and water at 100°.

$$CH_2\,.\,Br\,.\,CHBrCH_3 \longrightarrow CH_2{=}CH\,.\,CH_3$$

It will be recalled that Thiele's[6] original method for the preparation of butadiene was to heat the tetrabromide with zinc and alcohol. Finkelstein[7] has modified the reaction by complete elimination of the metallic factor, taking advantage of the instability of $\alpha\beta$-di-iodo compounds. Thus, ethylene is obtained by heating ethylene dibromide with a solution of sodium iodide in acetone

$$CH_2Br\,.\,CH_2Br \longrightarrow CH_2I\,.\,CH_2I \longrightarrow CH_2{=}CH_2 + I_2$$

(2) The direct reduction of halides by hydrogen can be accomplished catalytically, using platinum or palladium on some indifferent support—barium sulphate[8] or calcium carbonate.[9] An alkali is usually employed to neutralise the halogen acid formed during reduction.

---

[1] Thiele, Peter and Haackh, *Ann.*, 1909, **369**, 149 and 135.

[2] Gladstone and Tribe, *J.C.S.*, 1873, **26**, 445.

[3] Zelinski, *Ber.*, 1901, **34**, 2801.

[4] Clarke, *J.A.C.S.*, 1908, **30**, 1147; 1909, **31**, 113.

[5] Linnemann, *Ber.*, 1877, **10**, 1113.

[6] Thiele, *Ann.*, 1899, **308**, 339.

[7] Finkelstein, *Ber.*, 1910, **43**, 1530.

[8] Rosemund and Zetsche, *ibid.*, 1918, **51**, 578.

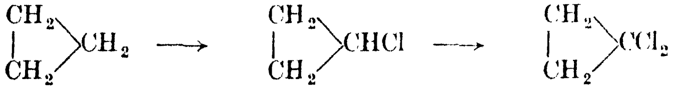
[9] Bush and Stöve, *ibid.*, 1916, **49**, 1063.

Attention has already been drawn to the tendency towards olefine formation in *secondary-* and *tertiary*-halides when heated with bases ; if water alone be used to effect hydrolysis the amount of olefine is decreased but not entirely eliminated. *Tertiary*-halides react readily with water and advantage is taken of this fact to estimate *tertiary*-halides in mixtures. Heated with water under reflux for a short time hydrolysis of the *ter*-halides is complete ; that of the *n*- and *secondary*-halides negligible ; titration of the halogen acid is therefore a means of indicating the amount of *tertiary*-halide in the original mixture.[1]

It is not proposed, in this volume, to deal with the interaction of halides and metals, this topic being considered in Chapter XI, Vol. II (" The Organo-metallic Compounds "), or with their reactions with ammonia, a subject more suitably treated under the heading of ' Amines '.

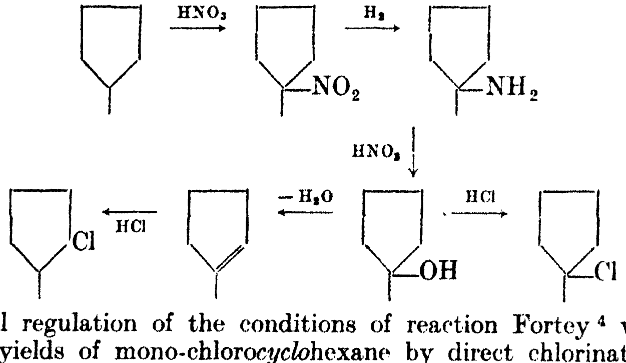
Halogen Derivatives of *Cyclo*paraffins

The chlorination of *cyclo*propane proceeds normally to a mono-chloro-derivative, together with some dichloro*cyclo*propane, probably the 1, 1-derivative[2] (29a)



(29a)

At the same time, some rupture of the ring takes place and chlorinated propanes are obtained, chiefly 1, 3-dichloropropane. Practically nothing is known about the chloro- derivatives of *cyclo*butane and *cyclo*pentane, although a 1-chloro-1-methyl *cyclo*pentane was obtained by Markownikov[3] by a roundabout method from the 1-nitro derivative. The corresponding 2-chloro-1-methyl *cyclo*pentane was also prepared ; the scheme of preparation of these two compounds is shown below in outline :—



By careful regulation of the conditions of reaction Fortey[4] was able to obtain good yields of mono-chloro*cyclo*hexane by direct chlorination, and it may also be obtained from *cyclo*hexanol by replacement of the hydroxyl group in the usual way. On the other hand, chloro*cyclo*hexane can be obtained almost quantitatively in a few minutes by the action of the theoretical amount of sulphuryl chloride on *cyclo*hexane in the presence of a trace of benzoyl peroxide.[5] Chlorination at 0° in diffused sunlight gives a complex mixture of chloro- derivatives from which Sabatier and Maihle[6] isolated two dichloro*cyclo*-hexanes, and three trichloro- derivatives, one of which was characterised as *s*-trichloro*cyclo*hexane.

---

[1] Michael and Leupold, *Ann.*, 1911, **379**, 287.

[2] Gustavson, *J. Pr. Chem.*, 1890 (2), **42**, 495.

[3] Markownikov, *Ann.*, 1899, **307**, 335.

[4] Fortey, *J.C.S.*, 898, **73**, 1932.

[5] Kharasch and Brown, *J.A.C.S.*, 1939, **61**, 2142.

[6] Sabatier and Maihle, *Ann. Chim.*, 1907 (8), **10**, 535.

The latter can be converted by further chlorination to the solid 1, 2, 4, 5-tetrachloro*cyclo*hexane.

All the five isomeric chloromethyl*cyclo*hexanes were prepared by Sabatier and Maihle, but their properties are not remarkable. The physical properties of a few of the chlorinated *cyclo*paraffins are shown in Table VI.

TABLE VI

Compound	B.P.	Density
Chloro*cyclo*propane	43°	—
1, 1-Dichloro*cyclo*propane . . .	75°	d_4^{15} 1·206
1-Chloro-1-methyl*cyclo*pentane . .	123°	—
2-Chloro-1-methyl*cyclo*pentane . .	126°	d_0^0 0·928
Chloro*cyclo*hexane	141-142°	d_0^0 0·991
1, 2-Dichloro*cyclo*hexane . . .	112-3°/50 mm.	d_0^0 1·222
1, 3, 5-Trichloro*cyclo*hexane . .	— m. 66°	d_0^0 1·510
1, 2, 4, 5-Tetrachloro*cyclo*hexane .	— m. 173°	—

AROMATIC HALOGEN COMPOUNDS

A description has already been given of the production of chlorobenzene by the direct chlorination of the hydrocarbon in the presence of iron (p. 62). Continuation of chlorination gives *o*- and *p*-dichlorobenzene (practically no *m*-derivative is formed) and further chlorination gives mainly the 1, 2, 4- with some 1, 2, 3- and traces of 1, 3, 5-trichlorobenzene, followed by 1, 2, 4, 5-tetrachloro-, pentachloro- and, finally, hexachlorobenzene.[1] The physical properties of these substances are given below in Table VII.

TABLE VII

Name	Formula	M.P.	B.P.	Corresponding BROMINE Compounds		Corresponding IODINE Compounds	
				M.P.	B.P.	M.P.	B.P.
Chlorobenzene . . .	C_6H_5Cl	— 45°	132°	— 31°	155°	— 30°	188°
1, 2-Dichlorobenzene .	$C_6H_4Cl_2$	—17·6°	180°	+ 7·8°	224°	+ 27°	286°
1, 3-Dichlorobenzene . .	$C_6H_4Cl_2$	—24·8°	172°	— 6·5°	219·4°	40°	285°
1, 4-Dichlorobenzene .	$C_6H_4Cl_2$	— 53°	173°	89°	219°	129°	285°
1, 2, 3-Trichlorobenzene .	$C_6H_3Cl_3$	53°	219°	87°	—	116°	—
1, 2, 4-Trichlorobenzene .	$C_6H_3Cl_3$	17°	213°	44°	275°	91·4°	—
1, 3, 5-Trichlorobenzene .	$C_6H_3Cl_3$	63°	208°	119°	278°	184·4°	—
1, 2, 3, 4-Tetrachlorobenzene	$C_6H_2Cl_4$	46°	254°	—	—	136°	—
1, 2, 3, 5-Tetrachlorobenzene	$C_6H_2Cl_4$	50°	246°	98°	329°	148°	—
1, 2, 4, 5-Tetrachlorobenzene	$C_6H_2Cl_4$	137°	244°	175°	—	254°	—
Pentachlorobenzene . .	C_6HCl_5	86°	276°	116°	—	172°	—
Hexachlorobenzene . .	C_6Cl_6	226°	326°	315°	—	decomp. 140-150°	—

Apart from direct chlorination, there are two main methods by which chlorobenzene derivatives may be prepared :—

(*a*) by the treatment of phenols with phosphorus pentachloride, a reaction which is seldom satisfactory on account of the difficulty of replacement of phenolic hydroxyl groups, and also on account of some chlorination which takes place ; in addition, part of the phenol is completely destroyed.

---

[1] Jungfleisch, *Ann. Chim.*, 1868 (4), **15**, 264, 277, 283, 287 ; Willgerodt, *J. Pr. Chem.*, 1887 (2), **35**, 391.

(*b*) The development of Sandmeyer's method. In 1884 Sandmeyer was trying to obtain phenylacetylene from aniline diazotised in hydrochloric acid and cuprous acetylide; instead of the hoped-for product he obtained a good yield of chlorobenzene, and on investigating the matter further found that the active agent was cuprous chloride.[1] The method is a general one, and is capable of very wide application for the preparation of both chlorine and bromine derivatives of aromatic compounds. Almost any amino- compound capable of diazotisation will give the reactions :—

$$C_6H_5N_2Br \xrightarrow{Cu_2Br_2} C_6H_5Br + N_2$$
$$C_6H_5N_2Cl \xrightarrow[Cu_2Cl_2]{} C_6H_5Cl + N_2$$

In replacement by bromine it is necessary to diazotise in hydrobromic acid and to employ cuprous bromide as a catalyst.

The mechanism of the reaction is obscure and will be discussed in detail in Chapter III of Vol. II. It may be added here, however, that Lellmann and Remy,[2] and Hantzsch,[3] obtained crystalline double compounds between the aryl diazonium halide and cuprous halide, and held the view that the decomposition of the double compound gave rise to the aryl halide.

The inclusion of the decomposition of the diazo compounds in the presence of potassium iodide in the Sandmeyer series is incorrect, as the reaction was discovered by Griess himself eighteen years earlier in 1866.[4] The success of the reaction is independent of the presence of copper or its salts, and proceeds

$$RN_2Cl + KI \longrightarrow RI + N_2 + KCl$$

The direct bromination of benzene proceeds similarly to the chlorination, but more reluctantly; the formation, for example, of bromobenzene requires heat and a suitable bromine carrier (iron); the direct iodination of benzene cannot be carried out, and a mixture of iodine and nitric acid is used, which forms iodic acid, the reaction then proceeding :—

$$5C_6H_6 + 4I + HIO_3 \longrightarrow 5C_6H_5I + 3H_2O$$

d-di-iodobenzene can be obtained by continuing the reaction.

In general it may be said that the halogen derivatives of benzene are very stable, holding their halogen atoms very firmly; stern measures are necessary to make chlorobenzene react with caustic alkalies or ammonia, a temperature of 300° and concentrated caustic alkali being required in the former instance, and autoclave pressure and 200° temperature in the latter. The removal of halogen, particularly iodine, by copper powder to form di-aryl compounds has already been dealt with (pp. 180 ff.). The reluctance to react is not, however, manifested in the case of the Grignard reagents, chloro- and bromo-benzene forming Grignard reagents normally, especially when 'started' with iodine or Gilman's catalyst; indeed, dry chlorobenzene and magnesium were shown by Gilman to form a Grignard compound in the absence of a solvent.

1, 2, 4-Trichlorobenzene is obtained by the action of boiling alkaline solutions on hexachloro*cyclo*hexane. If benzene be allowed to become saturated with chlorine in sunlight and the absence of a carrier, 'benzene hexachloride' (hexachloro*cyclo*hexane) (30) is obtained; a peculiar substance existing in several stereoisomeric forms. When heated with alkalies 1, 2, 4-trichlorobenzene is produced (33). The course of the reaction is most probably through the two intermediate stages (31) and (32). It will be observed that the first of these offers no alternative since the original molecule is symmetrical; the loss of the second molecule of hydrogen chloride could take place in several ways, but it appears that the allylic chlorine (marked * in (31)) is the most active, leading to the formation of (32), from which the elimination of a further molecule of hydrogen chloride must of necessity produce 1, 2, 4-trichlorobenzene.

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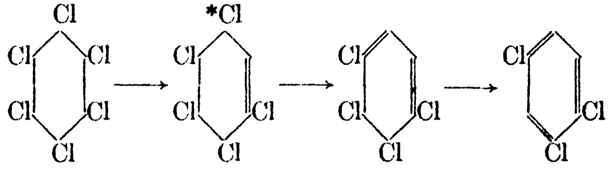
[1] Sandmeyer, *Ber.*, 1884, **17**, 2650.
[2] Lellmann and Remy, *ibid.*, 1886, **19**, 810.
[3] Hantzsch, *ibid.*, 1895, **28**, 1751.
[4] Griess, *Ann.*, 1866, **137**, 56; *Ber.*, 1868, **1**, 190; 1885, **18**, 961.



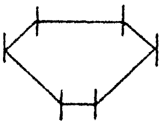
(30) (31) (32) (33)

Recently, it has been shown that certain of the more highly chlorinated cyclic and aralkyl hydrocarbons are of outstanding value in the control of insect pests. Of the more successful of these, γ-hexachloro*cyclo*hexane ('Gammexane') is a member of the group just described, whilst 1, 1'-*bis* (4-chlorophenyl)-2, 2, 2-trichloroethane ('D.D.T.') is a more complex compound.

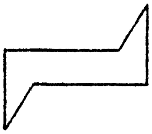
The original discovery by Faraday [1] in 1825 of a solid highly chlorinated derivative of his 'bicarburet of hydrogen' (benzene) was followed during nearly a century by occasional references by Mitscherlich, Peligot and Laurent, Meunier and Matthews to its properties and isomeric forms. In 1912 v. d. Linden [2] demonstrated that four distinct isomeric forms of benzene hexachloride existed :—

	v.d. Linden's m. pts.	J. S. Smart's m. pts.
α-form	158°	157·5–158°
β-form	>200°	309°
γ-form	108–111°	112·5°
δ-form	129–132°	138–139°

The more recent work of J. S. Smart [3] has lately resulted in methods by which these four isomers may be obtained in a state of purity. Considerable difficulty has been experienced in ascribing specific structures to these isomers. If the *cyclo*-hexane ring be regarded as planar (33a) there will be at least eight *cis-trans-* isomers possible; but, as Hassel and Kringstad [4] proved by X-ray analysis and examination of dipole moment, *cyclo*hexane consists almost exclusively of the *trans-* (strainless) ring form (33*b*), from which the hexachloride isomers are, presumably, derived. Of the sixteen possible configurations which can arise from this concept, only four structures are probable (one of which shows asymmetry of a type to give *d-* and *l*-forms) the others being excluded



(33a)



(33b)

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[1] Faraday, M., *Phil. Trans.*

[2] v. d. Linden, *Ber.*, 1912, **45**, 236.

[3] See Slade, *Chem. and Ind.*, 1945, 316.

[4] Hassel and Kringstad, *Tids. Kemi. Bergvessen*, 1930, **10**, 128.

by considerations of strain. These forms are shown in Fig. V with their tentative correlation with the four known isomers. These forms are more easily understood from solid models, and the reader is recommended to build up the structures with Fisher-Hirschfelder units; the impossibility of having, for example, all six chlorine atoms on the upper plane will then become obvious.

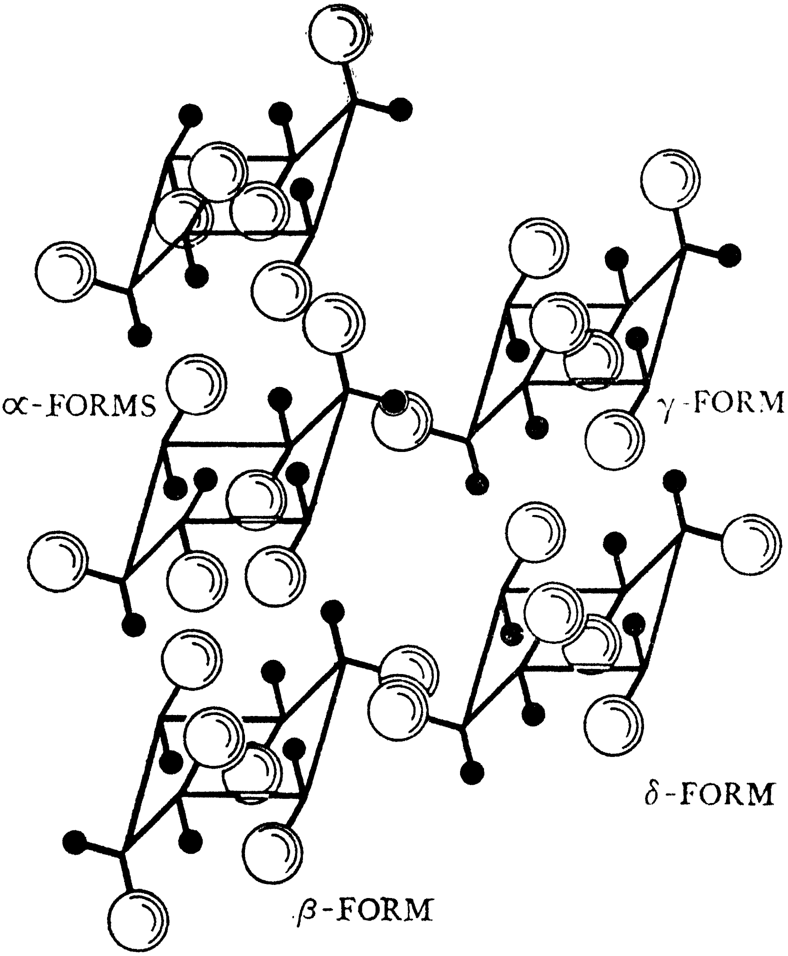
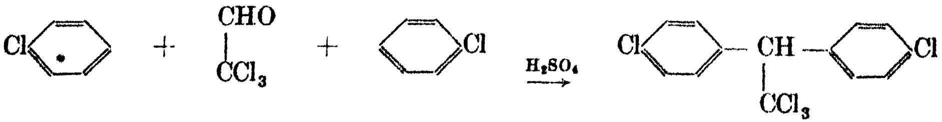


FIG. V.—The Hexachloro-trans-cyclohexanes.

It was soon apparent to the investigators that the γ-isomer was the most effective insecticidally; lice, household flies, yellow fever mosquitoes and locusts are among the many forms of insect that are killed by extremely low concentrations of 'Gammexane'.

D.D.T. or dichlorodiphenyltrichloroethane, was first prepared by Zeidler[1] in 1874, by the condensation of chloral and chlorobenzene in strong sulphuric acid :—



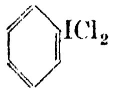
a method still used for its production. Its value as an insecticide was recognised in the period 1930–1935, and it was used in Switzerland for the destruction

[1] Zeidler, *Ber.*, 1874, 7, 1181

of flies, lice and similar pests. The recent war has brought about a considerable development of its use[1] in this respect. The application of one millionth part of a γ (i.e. 10^{-12} gm.) per square centimetre of insect surface is stated to be fatal.

POLYVALENT ARYL IODINE COMPOUNDS

Much of our knowledge of this group of substances is due to Willgerodt, whose monograph (see Appendix I) is an authoritative summary of the data up to 1914. Willgerodt[2] obtained the first member of the series by submitting a solution of iodobenzene in chloroform to a slow stream of chlorine, cooling meanwhile. Phenyl iododichloride (34) separated in light yellow needles



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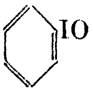

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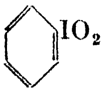

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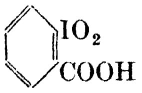


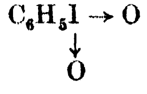
(37)

It is a moderately stable substance, but liberates iodine from solutions of potassium iodide, and in moist air decomposes to form iodosobenzene (35), an unstable substance which on boiling with water suffers a disproportionating reaction to give iodobenzene and iodoxybenzene (36). Attempts to recrystallise iodosobenzene from glacial acetic acid led to the formation of the diacetate, $C_6H_5I(OCOCH_3)_2$, a crystalline salt of the hypothetical $C_6H_5I(OH)_2$.

Little use has been made of the higher valency[3] compounds of iodine in organic chemistry; mention may, however, be made of the use of the calcium salt of *o*-iodoxybenzoic acid (37) (prepared from anthranilic acid), in medicine, where it appears to exert a palliative action in rheumatic conditions. In addition the iodoxy compounds have led to a knowledge of the iodonium compounds. Thus, iodoxy- and iodoso-benzene warmed with a suspension of silver oxide yield a water-soluble, strongly basic diphenyl iodonium hydroxide:—

$$C_6H_5IO + C_6H_5IO_2 + H_2O \xrightarrow{Ag_2O} (C_6H_5)_2IOH + HIO_3$$

the iodic acid is removed by the passage of sulphur dioxide, and on addition of potassium iodide, crystals of diphenyliodonium iodide separate. The reaction is a general one, and other salts of the aryl iodonium bases can readily be obtained. The electronic significance of these compounds is interesting, and they may be formulated as follows :—

(*a*) $[C_6H_5ICl]^+Cl^-$	Iodobenzene temporarily takes on a Cl_2 molecule, forming a decet of electrons round iodine; this stabilises to a covalency with the complex ion $[C_6H_5ICl]^+$ and an ionic Cl^-.
(*b*) $C_6H_5I \rightarrow O$	A second co-valency is introduced.
(*c*)  $\begin{array}{l} C_6H_5I \rightarrow O \\ \quad\;\;\downarrow \\ \quad\;\;O \end{array}$	A third co-valency is introduced.
(*d*) $[(C_6H_5)_2I]^+I^-$	In order to accept the second aryl group and maintain the octet, an electron must be expelled yielding the ionic structure shown.

---

[1] West and Campbell, *Chem. and Ind.*, 1945, 154.

[2] Willgerodt, *J. Pr. Chem.*, 1886 (2), **33**, 155 ; *Ber.*, 1893, **26**, 1553, 1947 ; 1896 ; **29**, 1568 ; *J. Pr. Chem.*, 1905 (2), **71**, 540.

[3] Masson, Race and Pounder, *J.C.S.*, **1935**, 1669.

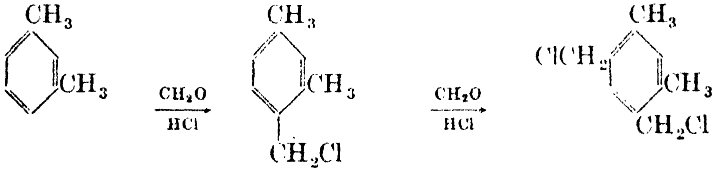
HALOGENATED HOMOLOGUES OF BENZENE

When homologues of benzene are chlorinated the reaction takes one of two courses, substitution either of the nucleus or side-chain. It has already been stated (p. 88) that certain catalysts favour nuclear substitution and others direct entering chlorine atoms almost exclusively into the side-chain. The latter is more usual, and pure samples of nuclear halogen substituted derivatives of toluene and xylene are best prepared from the corresponding amine *via* Sandmeyer's reaction. On the other hand, direct chlorination of the side-chain of toluene may be progressively carried out with the formation of

Benzyl chloride	$C_6H_5CH_2Cl$	b. 179°	m. – 39°
Benzal chloride	$C_6H_5CHCl_2$	b. 205°	m. – 7°
Benzotrichloride	$C_6H_5CCl_3$	b. 220°	m. – 5°

The reaction is carried out in the absence of catalyst, but is favourably influenced by sun or ultra-violet light. Industrially, the light from mercury vapour lamps in quartz containers is used to hasten the reaction.

An alternative method of introducing a $-CH_2Cl$ side-chain into aromatic nuclei is to react an alkylbenzene with formaldehyde in the presence of hydrogen chloride; the $-CH_2Cl$ group enters *para-* or *ortho-* to existing alkyl groups; e.g., *m*-xylene gives an ω-chloro-ψ-cumene (38)



(38) (39)

further treatment leads to the entry of a further $-CH_2Cl$ group, leading to a durene derivative (39).

The halogen of side-chain derivatives is very reactive, equalling, if not exceeding, the reactivity of the corresponding alkyl halide. Thus, benzyl chloride reacts readily with dilute alkalies yielding benzyl alcohol; with sodium cyanide to give phenyl acetonitrile; with potassium or sodium iodide in acetone a metathesis is obtained to the alkali chloride and benzyl iodide, a somewhat lachrymatory solid, m. 24°. As with alkyl iodides the side-chain halides of benzene homologues readily form Grignard compounds.

Benzal chloride is produced industrially to serve as a raw material for the production of benzaldehyde which is produced from it by boiling with milk of lime :—

$$C_6H_5 . CHCl_2 + Ca(OH)_2 = C_6H_5CHO + CaCl_2 + H_2O$$

Benzotrichloride is not intentionally produced industrially, but always occurs in the chlorination mixture when working for benzal chloride. On hydrolysis it yields benzoic acid, which remains behind as the calcium salt when the

$$C_6H_5 . CCl_3 + 2H_2O \longrightarrow C_6H_5COOH + 3HCl$$

mixed chlorides are used and the benzaldehyde is steamed out; acidification of the calcium liquors after filtration yields benzoic acid.

Of the aryl derivatives with unsaturated halogen-substituted side-chains, only bromostyrene, $C_6H_5CH{=}CHBr$, has attained industrial importance. It is obtained by boiling cinnamic acid dibromide with sodium carbonate solution :—

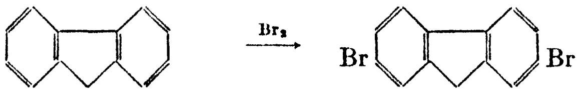
$$C_6H_5CHBrCHBrCOONa \longrightarrow C_6H_5CH{=}CHBr + NaBr + CO_2$$

It has an intense hyacinth odour and is used in perfumery for this quality.

Halogen Derivatives of other Hydrocarbons

Direct chlorination of naphthalene gives 95 per cent. of the α- and 5 per cent. of the β-chloro- derivative. They are readily separated by crystallisation, but when β-chloronaphthalene is required for synthetic work it is best made by the cuprous chloride Sandmeyer reaction from β-naphthylamine. Progressive chlorination of naphthalene yields the 1, 4- and 1, 5- dichloro-compounds with small amounts of other isomers. All the ten dichloronaphthalenes have been prepared in connexion with orientation studies in the naphthalene series. The properties of some halogen derivatives of naphthalene are given in Table VIII.

In the case of fluorene it is interesting to note that chlorination and bromination takes place in the ' 2, 7 ' positions



just as if the parent diphenyl structure was present.

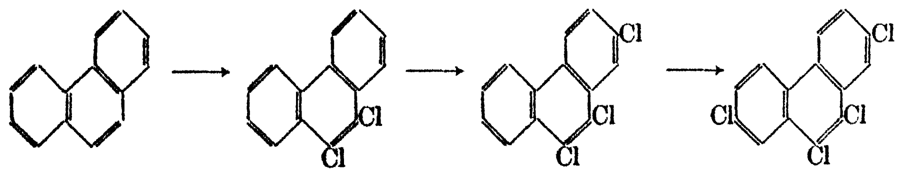
TABLE VIII

Substance	Substituent			
	F	Cl	Br	I
α-Monohalogenonaphthalene	— b. 216°	— b. 263°	m. 5° b. 279°	— b. 305°
β-Monohalogenonaphthalene	m. 59° b. 213°	m. 56° b. 265°	m. 59° b. 282°	m.54·5° b.303°

Dichloronaphthalenes

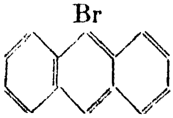
Orientation	1, 2-	1, 3-	1, 4-	1, 5-	1, 6-
Properties	m. 37° b. 281°	m. 61° b. 289°	m. 68° b. 287°	m. 107°	m. 49°
Orientation	1, 7-	1, 8-	2, 3-	2, 6-	2, 7-
Properties	m. 64° b. 286°	m. 88°	m. 120°	m. 136° b. 285°	m. 114°

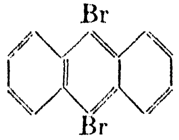
Phenanthrene, on the other hand, halogenates in the 9, 10-positions first, giving the 9, 10- dichloro- derivative (41), further chlorination produces a 2, 9, 10- trichloro- (42) and some 2, 7, 9, 10-tetrachlorophenanthrene (43),



(40) (41) (42) (43)

indicating that the next points of attack are the potential ' diphenyl ' positions ' 2' and ' 7 '. In a similar manner the ' 9 ' and ' 10 ' positions are the first points of attack in anthracene, the 9-bromo and 9, 10-dibromo being the first formed substitution products (44)





(44)

APPENDIX I

LITERATURE REFERENCES ON HALOGEN COMPOUNDS

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CHAPTER V

THE ALCOHOLS, PHENOLS AND ETHERS

> " Having now prepared this *aqua vitae* by distillation and rectification (take care that thou comest not near with a light during the process, and doest thyself damage), place in a still to every quart of this prepared *aqua vitae* a quarter of a pound of well calcined *sal tartari*. Adapt this to a good sized alembic and distil in the water bath."
>
> —Basil Valentine.

The material of this chapter is divided for convenience into the following sections :—

Monohydric alcohols and phenols.
Dihydric alcohols and phenols.
Trihydric alcohols and phenols.
Polyhydric alcohols.
Halogen substituted alcohols and phenols.
The ethers.

Hydroxyl compounds with other functional groups, such as the hydroxy acids, hydroxy aldehydes and ketones, are discussed under the appropriate section in the chapter dealing with the second functional group.

Monohydric Alcohols

Ethanol, commonly called alcohol, has been known as the active ingredient of fermented spirituous liquors since time immemorial. Distilled liquors containing up to 50-80 per cent. of alcohol were also known in antiquity, and as the quotation at the head of this chapter indicates, the art of preparing alcohol of nearly 100 per cent. strength was known some four hundred years ago. The synthesis of ethanol in 1855 by Berthelot [1] was of considerable interest, although not the first synthetic preparation ; its interest, at that time, lay in the fact that from inorganic substances lime, carbon and water, acetylene could be obtained and converted almost directly to alcohol, then regarded only as a fermentation product. Various alcohols occur in natural products, mainly the fruits of plants, increasing in quantity as ripeness advances.

General methods of preparation include :—

(1) *Hydrolysis and saponification.* These two terms are frequently used as though they are synonymous ; the latter should be reserved for the action of alkalies on esters, whilst the former is to be used for splitting an ester into an acid and an alcohol by water.

The two processes are sufficiently familiar not to need detailed description, and an account of the relation between structure and ease of hydrolysis is given in Vol. III. It may be added here that the use of baryta for the hydrolysis of esters has much to recommend it, particularly with aliphatic compounds ; no coloured by-products are obtained, and the reaction proceeds quite smoothly. It is, moreover, easy to remove the barium from the residue after removal of the alcohol, by addition of sufficient sulphuric acid to ensure its complete precipitation.

(2) Alcohols are also prepared by Berthelot's original method, which involves the addition of water to the double bond of an olefine. This is

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[1] Berthelot, *Ann. Chem. Phys.*, 1885, **43**, 385.

not a direct action, but, in the process referred to, is probably preceded by the formation of a sulphuric ester, which is hydrolysed to the alcohol. Thus, the simplest case, that of ethylene, involves the formation of an ethyl sulphuric acid (1) which is hydrolysed to ethanol :—

$$CH_2{=}CH_2 + H_2SO_4 \xrightarrow{H_2SO_4} \underset{(1)}{CH_3 . CH_2O . SO_3H} \xrightarrow{H_2O} CH_3 . CH_2OH + H_2SO_4$$

Since the discovery of this process in 1855, it has been the subject of considerable investigation directed towards its adaptation as a process for the industrial recovery of ethylene. The occurrence of ethylene in coke-oven gas led to attempts by the Skinningrove Iron Co. to extract this valuable fraction by sulphuric absorption, followed by conversion to ethanol. The process was technically, but not economically, successful. The economic fault lay to some extent in the difficulty and cost of obtaining a small quantity of ethylene in high yield from a large volume of gas. It is preferable and economically practicable to extract this ethylene from the hydrocarbon fraction obtained when the coke-oven gas is worked up for its hydrogen in an ammonium sulphate plant. The treatment of the ethylene rich fraction then resembles the working up of ethylene from cracker or natural gas, and is a good source of industrial ethanol. It must not, however, be thought that ethyl sulphuric acid is the only product of reaction between ethylene and sulphuric acid. Some isethionic acid, $CH_2OH . CH_2 . SO_3H$, is always produced.

The effect of catalysts, particularly copper and vanadium[1] (the former in the cuprous state) is materially to increase the rate of absorption of ethylene by sulphuric acid (see also p. 88), and if the passage of ethylene is continued beyond the point of formation of the ethyl sulphuric acid, neutral diethyl sulphate results. This is, of course, no detriment to the formation of ethanol, as both neutral and acid sulphates are readily hydrolysed.

Attention has also been given to the direct hydration of ethylene, and Horsley[2] claims the use of a special cadmium phosphate catalyst for speeding up the desired reaction :—

$$CH_2 = CH_2 + H_2O \longrightarrow CH_3CH_2OH.$$

(3) The formation of alcohols from halogen compounds also constitutes a valuable method of preparation. The reaction can, in certain cases, be effected by water alone at 100°, or preferably at a higher temperature, using an autoclave :—

$$R . Cl + H_2O \rightleftharpoons R . OH + HCl.$$

The reaction is reversible, and can be made more effective by the use of an alkali or carbonate (e.g. $CaCO_3$) to remove hydrochloric acid as formed. A good example of the use of this process is the hydrolysis of benzyl chloride with milk of lime to benzyl alcohol.

(4) Alcohols may also be produced by desalkylation of ethers with concentrated hydrobromic or hydriodic acids. This is, of course, the basis of the Zeisel reaction. Sulphuric acid is also capable of effecting the removal of alkyl groups from ethers, but is seldom used as it induces a number of complicating side-reactions.

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[1] Lebeau, Damiens and Loisy, *C.R. Cong. des Comb. liq.*, 1922, 664 ; also *C.R.*, 1920, **171**, 50 and 1385 ; Damiens, *Bull. Soc.*, 1923, **33**, 80.

[2] Horsley (to I.C.I.), E.P., 369,216, 1931.

(5) A reaction of considerable theoretical importance, but of little practical value owing to general inaccessibility of the raw materials, is the formation of alcohols by the action of nitrous acid on primary aliphatic amines

$$R.NH_2 + HNO_2 \longrightarrow R.OH + N_2 + H_2O.$$

The reaction is by no means as simple as indicated by the equation above, and is further complicated by the peculiar isomerisation which takes place during its course; thus if *n*-butylamine is treated with nitrous acid practically no *n*-butanol is formed; the main product is 2-butanol.[1] A similar rearrangement is met with when substituted allylamines are subjected to nitrous acid treatment, e.g. methyl allylamine,

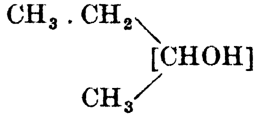
$$CH_3.CH{=}CH.CH_2NH_2,$$

gives rise to butene-1-ol-3, $CH_3.CH(OH)CH{=}CH_2$, as well as the expected butene-2-ol-1.

The methods for preparing alcohols so far described have not been confined to any one class of saturated monohydric alcohols. It is now necessary to distinguish between those processes capable of producing primary, secondary and tertiary alcohols. The best way of regarding primary, secondary and tertiary alcohols is in connexion with the carbinol group [ ] below. The carbinol group of a primary alcohol

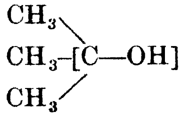
$CH_3.CH_2.CH_2[CH_2OH]$

Primary



$$\begin{array}{l} CH_3.CH_2\diagdown \\ \qquad\qquad [CHOH] \\ CH_3\diagup \end{array}$$

Secondary



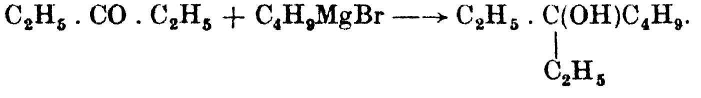
$$\begin{array}{l} CH_3\diagdown \\ CH_3{-}[C{-}OH] \\ CH_3\diagup \end{array}$$

Tertiary

is attached to a single carbon atom; that of a secondary to two, and that of a tertiary to three carbon atoms. In preparing secondary and tertiary alcohols the organo-metallic reactions are of considerable importance. Thus, the action of zinc dimethyl upon acetone is to produce trimethyl carbinol (1):—

$$CH_3.CO.CH_3 + Zn(CH_3)_2 \longrightarrow \underset{(1)}{(CH_3)_3C.OH.}$$

The use of zinc alkyls is inconvenient, and the use of Grignard reagents has almost universally taken their place. Thus, diethyl ketone reacts with magnesium butyl bromide to give 3-ethylheptanol-3:—

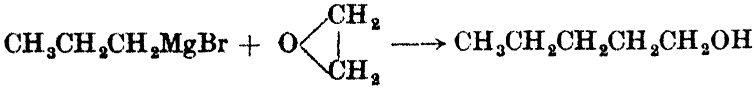


$$C_2H_5.CO.C_2H_5 + C_4H_9MgBr \longrightarrow C_2H_5.\underset{\displaystyle C_2H_5}{\underset{|}{C}}(OH)C_4H_9.$$

Certain ketones, e.g. hexamethylacetone, $(CH_3)_3C.CO.C(CH_3)_3$, do not react in this way with the Grignard reagent, reduction to a secondary alcohol taking place, $(CH_3)_3C.CH(OH).C(CH_3)_3$. Aldehydes react with the Grignard reagent to give secondary alcohols, although the yield is often unsatisfactory:—

$$CH_3CH_2CH_2CHO + EtMgBr \longrightarrow CH_3CH_2CH_2CH(OH)CH_2CH_3.$$

Most valuable in the formation of synthetic primary alcohols is the interaction of ethylene oxide and the Grignard compound:—

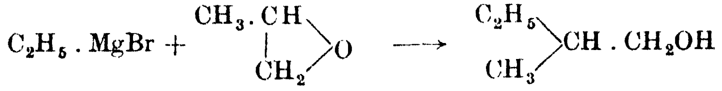


$$CH_3CH_2CH_2MgBr + O\left\langle\begin{array}{l}CH_2\\ |\\ CH_2\end{array}\right. \longrightarrow CH_3CH_2CH_2CH_2CH_2OH$$

---

[1] Meyer, Bartieri and Forster, *Ber.*, 1877, **10**, 130.

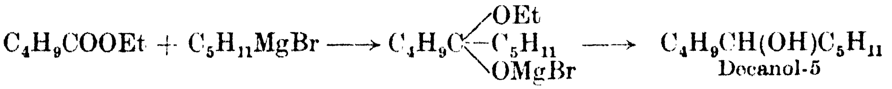
The reaction gives good yields, and increases the length of the carbon chain by two units. If a substituted ethylene oxide is used (as propylene oxide) the alcohol obtained is primary but arborescent [1] (2).



$$C_2H_5 . MgBr + \begin{matrix} CH_3.CH \\ | \\ CH_2 \end{matrix}\!\!>O \longrightarrow \begin{matrix} C_2H_5 \\ CH_3 \end{matrix}\!\!>CH . CH_2OH$$

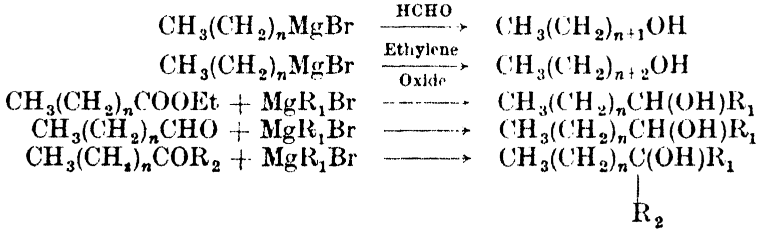
(2)

There is an additional method for obtaining primary alcohols from the Grignard reagent, namely, by the action of formaldehyde. Gaseous formaldehyde reacts readily, as also does the mixture of polymers known as ‘ paraform ’. It should be added that esters are also capable of reacting with the Grignard compound to give secondary alcohols, thus :—



$$C_4H_9COOEt + C_5H_{11}MgBr \longrightarrow C_4H_9C\begin{matrix} \diagup OEt \\ -C_5H_{11} \\ \diagdown OMgBr \end{matrix} \longrightarrow \underset{\text{Decanol-5}}{C_4H_9CH(OH)C_5H_{11}}$$

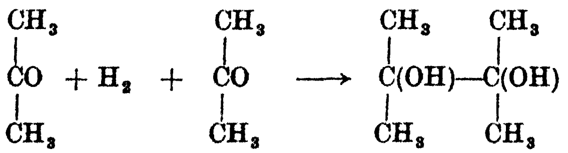
The decompositions of the Grignard reagent to give alcohols are summarised in the following diagram :—



$$\begin{array}{rcl} CH_3(CH_2)_nMgBr & \xrightarrow{HCHO} & CH_3(CH_2)_{n+1}OH \\ CH_3(CH_2)_nMgBr & \xrightarrow[\text{Oxide}]{\text{Ethylene}} & CH_3(CH_2)_{n+2}OH \\ CH_3(CH_2)_nCOOEt + MgR_1Br & \longrightarrow & CH_3(CH_2)_nCH(OH)R_1 \\ CH_3(CH_2)_nCHO + MgR_1Br & \longrightarrow & CH_3(CH_2)_nCH(OH)R_1 \\ CH_3(CH_2)_nCOR_2 + MgR_1Br & \longrightarrow & CH_3(CH_2)_n\underset{\underset{R_2}{|}}{C}(OH)R_1 \end{array}$$

(6) *Reduction Methods.*—It is obvious that the reduction of aldehydes yields primary alcohols ; reduction of ketones gives secondary alcohols. For carrying out these reductions catalytic processes are particularly valuable ; nickel and hydrogen will serve for the reduction, and for aldehydes of higher carbon number than 5, vapour-phase reduction with hydrogen in the presence of nickel is particularly successful. Raney nickel in the cold can be used for some aldehydes ; with platinum-black and hydrogen, aldehydes can be substantially reduced to the alcohol, only small quantities of the hydrocarbon being obtained ; on the other hand, ketones are almost entirely reduced to the hydrocarbon by these reagents.

Other methods can be used for these reductions and the commonly used reagents are sodium and alcohol, sodium amalgam, magnesium in the presence of aqueous mercuric chloride and the zinc-copper couple. It may be added that when a comparatively weak reducing agent, such as sodium amalgam is used for the reduction of ketones, the formation of pinacones (tetra-substituted ethylene glycols) is frequently experienced, as with acetone.



$$\begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{matrix} + H_2 + \begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{matrix} \longrightarrow \begin{matrix} CH_3 & & CH_3 \\ | & & | \\ C(OH) & — & C(OH) \\ | & & | \\ CH_3 & & CH_3 \end{matrix}$$

---

[1] Grignard, *C.R.*, 1903, **136**, 1261.

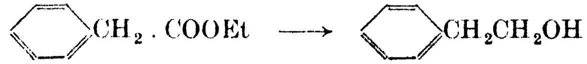
On the other hand, the stronger reagents not only reduce any aldehyde or keto groups present, but may also remove any unsaturated groups, leaving a saturated alcohol.

(7) The method of Bouveault and Blanc[1] is of inestimable value for the production of primary alcohols from the acids of similar carbon number. Thus if an acid be converted to its ester and reduced with alcohol and sodium, a good yield of the corresponding alcohol is obtained. The reaction proceeds :—

$$CH_3(CH_2)_nCOOH \xrightarrow[\text{Esterification}]{} CH_3(CH_2)_nCOOEt \xrightarrow[\text{Na + C}_2\text{H}_5\text{OH}]{} CH_3(CH_2)_nCH_2OH$$

The method is capable of extension to two classes of compounds of practical importance :—

(*a*) The aromatic substituted esters, e.g. phenylacetic ester (3)



(3) (4)

which gives phenyl-ethyl alcohol (4) free from isomeric substances and from chlorine compounds, as is necessary for its use in the perfumery industry.

(*b*) The half esters of dibasic acids are reduced by sodium and alcohol only at the esterified end, thus enabling the production of hydroxy acids, which are valuable starting materials for syntheses :—

$$\underset{\text{Acid pimelic ester}}{HOOC(CH_2)_5COOEt} \longrightarrow \underset{\text{Heptanol–7, acid–1}}{HOOC(CH_2)_5CH_2OH}$$

(8) In difficult cases monohydric alcohols can be obtained by the method of Simonini[2] whereby the silver salt of an acid is heated with iodine at 100°. The reaction leads to an ester (5)

$$2\,CH_3(CH_2)_7COOAg + I_2 \longrightarrow \underset{(5)}{CH_3(CH_2)_7COO(CH_2)_7CH_3}$$
$$\longrightarrow CH_3(CH_2)_7COOH + CH_3(CH_2)_6CH_2OH$$

which can be hydrolysed to an alcohol and the acid from which the process commenced ; the process is only used in cases where ordinary methods fail, or lead to an undesired isomeric change.

An interesting example of the application of Simonini's reaction is his synthesis of pentadecanol-1, thus :—

$$2\,C_{15}H_{31}COOAg + I_2 \longrightarrow 2AgI + CO_2 + C_{15}H_{31}COOC_{15}H_{31}$$
$$\longrightarrow C_{15}H_{31}COOH + C_{15}H_{31}OH$$

(9) Cannizzaro's Reaction has valuable possibilities in the aromatic field, e.g. the nitrobenzyl alcohols can be prepared from the corresponding aldehydes ; the method is merely to shake the aldehyde with a solution of potassium hydroxide, when reactions take place which are summarised by the equation

$$2R\,.\,CHO \xrightarrow{KOH} RCH_2OH + R\,.\,COOH$$

---

[1] Bouveault and Blanc, *Ber.*, 1898, **31**, 366.
[2] Simonini, *Monatsh.*, 1892, **13**, 321.

Separation of the two products is usually quite simple, as the acid dissolves as the potassium salt, whilst the alcohol remains undissolved, and may be extracted with a suitable solvent. It is held by many that the reaction takes place through the formation of an acyloin (6) which is later saponified to the acid and alcohol, e.g. :—

$$2\ C_6H_5CHO \longrightarrow \underset{(6)}{C_6H_5COCH(OH)C_6H_5} + KOH \longrightarrow C_6H_5COOK + HOCH_2C_6H_5$$

This is supported by the fact that in the presence of dilute alkalies aldehydes are known to form acyloins, which can be isolated and characterised; it is also known that the acyloins are, themselves, hydrolysed in the manner indicated above. There is, however, some evidence to show that the ester is formed, and Tischtchenko regarded the reactions as parallel :—

$$2\ R\ .\ CHO \longrightarrow RCOOCH_2R \longrightarrow R\ .\ COOH + HOCH_2R$$

This would make the reactions of Cannizzaro and Simonini of a similar type.

(10) An unusual method, of limited application, is that of Guerbert,[1] in which an alcohol is heated in a sealed tube to 240° with its sodium derivative; the primary alcohol with twice the original number of carbon atoms is formed :—

$$C_5H_{11}OH + C_5H_{11}ONa \longrightarrow \underset{\text{decanol-1}}{C_5H_{11}\ .\ C_5H_{10}OH} + NaOH$$

The alkali formed reacts with a further molecule of alcohol, giving the sodium salt of an acid and hydrogen :—

$$C_5H_{11}OH + NaOH \longrightarrow H_2 + C_4H_9COONa.$$

General Properties of the Alcoholic Hydroxyl

The reactions of alcohols, in so far as they are dependent on the hydroxyl group, are divisible into three classes. Those in which the hydroxyl group is replaced entirely, those in which the hydrogen only of that group is replaced, and addition reactions.

Examples of the first are :—

(*a*) Replacement by halogens.
(*b*) Esterification.

Of the second :—

(*a*) Formation of the alkoxide, e.g. NaOEt.
(*b*) Etherification.

And of the third :—

(*a*) The formation of urethanes.
(*b*) The formation of hemiacetals.

As so many examples of these reactions are encountered in discussing the individual alcohols, it is proposed to proceed immediately to this section.

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[1] Guerbert, *Ber.*, 1888, **21**, 487.

SOME INDIVIDUAL ALCOHOLS

Methanol.—It is claimed that the leaves of certain plants and trees (*Heracleum* and Lime) give off small quantities of methanol. There is less doubt about the presence in many plants of methyl esters of various types, of which the salicylate in *Gaultheria procumbens* is typical. None of these, however, can serve as a source of the alcohol for industrial purposes.

Until the last decade the main source of methanol was the spirituous liquor obtained during the distillation of wood. This, on rectification, gave a crude methyl alcohol, from which much fractionation could not entirely remove the accompanying acetone. The crude alcohol has been known and used for several hundred years. It was the subject of a series of researches by Robert Boyle, who in 1661 remarked of it :—

> " I took eight ounces of rectified spirit of box wood wherein the acetous and neutral spirit remained confounded, as they had been in the first distillation ; and having poured this upon a quantity of calcined coral, sufficient to satiate the acid corpuscles (which quickly fell to corrode it with noise and bubbles), we gently distilled it to dryness in a glass head and body, by which means we obtained of adiaphorus spirit but eight grains less than seven ounces and a half."

The distillation of wood, as an industry, grew considerably in the nineteenth century, and provided a fair supply of wood alcohol, which in its crudest state was used as a denaturant for ethanol (methylated spirit). The rectified methanol, although impure, was used for industrial purposes ; pure methanol for scientific work (an expensive substance) was obtained by the conversion of the crude alcohol to oxalate by boiling with anhydrous oxalic acid ; the purified oxalate was then decomposed with alkali and the methanol recovered and concentrated by fractionation.

Synthetic methods have now almost displaced the older methods of production from wood-alcohol. The processes which have been proposed for the synthetic production of methanol are as follows :—

(1) The formation of methyl chloride from the methane of natural gas, its separation and hydrolysis.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl \longrightarrow CH_3OH$$

(2) The formation of lithium or barium formate by the action of carbon monoxide on heated lithium or barium oxides ; followed by distillation of the formate under reduced pressure when methanol, mixed with various impurities, was formed. The old Badische Anilin und Soda Fabrik attempted to introduce this method industrially.

(3) The so-called Fischer-Tropsch process, in which carbon monoxide and hydrogen are caused to combine at high pressure in the presence of a catalyst

$$CO + 2H_2 \longrightarrow CH_3OH$$

Only the last process remains as a practical achievement, and is now operating on water-gas to produce a considerable tonnage of synthetic methanol which has proved a valuable chemical asset.

Methanol, owing to its simplicity of structure, has few reactions—it can be oxidised to formaldehyde, and by more strenuous treatment it can be converted to carbon dioxide and water. It is, however, more violently reactive than other alcohols, and whilst forming sodium or potassium derivatives, readily attacks aluminium and magnesium converting them to methoxides with liberation of hydrogen. The formation of magnesium methylate is used to render methanol anhydrous; a few grams of magnesium dissolved in as many litres of methanol, which has been rendered as near anhydrous as possible, will remove any residual water by the reaction

$$Mg(OCH_3)_2 + H_2O \longrightarrow 2CH_3OH + MgO$$

Methanol gives methyl chloride on treatment with hydrogen chloride, and on absorption in oleum and distillation yields dimethyl sulphate

$$CH_3OH + HCl \xrightarrow{ZnCl_2} H_2O + CH_3Cl$$
$$2CH_3OH + 2H_2SO_4 \longrightarrow 2CH_3 \,.\, HSO_4 \longrightarrow (CH_3)_2SO_4 + H_2SO_4$$

Ethanol.—All the ethanol of commerce, with a small exception, is manufactured from carbohydrate material—potatoes, grain or molasses by fermentation. The subject of fermentation is reserved for special treatment in Appendix II to this chapter, so that nothing further will be said on the subject here. Alcohol can, of course, be synthesised, but no synthetic process has yet proved an economic competitor to the fermentation method, although the sulphuric process is operating successfully in the U.S.A.

The most promising synthetic method for producing ethanol appears to be hydration of ethylene with sulphuric acid :—

$$CH_2{=}CH_2 + H_2O \xrightarrow[H_2SO_4]{} CH_3CH_2OH$$

This method was discovered in 1826 by Faraday[1] and Hennell.[2] Faraday ascertained that ethylene was absorbed by concentrated sulphuric acid, and Hennell, to whom he assigned the second part of the investigation, showed that by diluting Faraday's solution, ethanol was obtained. The process was rediscovered by Berthelot in 1855. It is probable that the most satisfactory method of utilising the process is to combine it with the synthesis of ammonia from coke-oven gas, using the ammonia to neutralise the dilute acid from the hydrolysis, giving ammonium sulphate. It should be possible to feed the concentrated sulphuric acid/ethylene absorbate into a column at about the half-way level, with ammonia admitted to one of the lower plates and to take off ethanol at the top, ammonium sulphate solution of crystallising strength at the bottom, and water somewhere between the centre and top plates.

The difficult question to settle in any process of this nature is the degree of purity required in the ethylene used; it appears that the Skinningrove and Bethune experiments failed economically, because of the large volumes of gas containing low ethylene percentages which it was necessary to handle. In a synthetic ammonia plant handling coke-oven gas, concentration of hydrocarbons becomes necessary, and a fractionation of these would not prove unduly difficult. On the other hand, pure ethylene from cracker gas can give ethanol at approximately the same cost as that from molasses.

The uses of ethanol are manifold; beverage spirit is in this and many other countries controlled by elaborate and strict Excise laws; all Excise calculation is carried out in terms of 'proof spirit', which was defined by Act 58 Geo. III, as "being such as shall at a temperature of 51° F. weigh exactly $\frac{12}{13}$ths part of an equal measure of distilled water". This works out at 49·3 per cent. by weight or 57·09 per cent. by volume. The terms "50° o.p." or "25° u.p." (the letters standing for 'overproof' and 'underproof') mean that, in the first case, 100 parts of the spirit require to be diluted with 50 of water in order to secure 'proof spirit'; and in the second that 100 volumes of the sample requires the removal of 25 parts of water to bring the spirit to 'proof strength'.

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[1] Faraday, *Phil. Trans.*, 1825, **115**, 448.

[2] Hennell, *ibid.*, 1826, **116**, 240; 1828, **118**, 365.

Although a considerable amount of alcohol is consumed in beverage form, far more is used industrially as a solvent, and raw material for synthetic processes; the chemist has only to recall the innumerable instances when he has used ethanol in laboratory procedure, to visualise its corresponding importance to the chemical industry. Much industrial alcohol is used in a 'denatured' form, i.e. in admixture with small amounts of crude wood-alcohol, or crude pyridine bases, which, whilst not interfering with solvent powers, prevents usage as or conversion to beverage spirit. In addition, 'un-denatured' alcohol can, under special licence, be used industrially where the denaturant would interfere with the process. There is, therefore, no reason why any industrial process requiring alcohol of any grade of purity should not be able to obtain it, free of beverage duty, always providing that no part of the alcohol is, or can be, used for potable purposes. Ethanol is used also as a component of anti-freeze mixtures, and in fuels for internal combustion engines; mixtures of alcohol, petrol and benzene afford a stable and successful fuel.

Absolute alcohol is best obtained by removing water from the industrial 96 per cent. spirit by azeotropic distillation with benzene. The following test is useful in ascertaining whether alcohol is really 'absolute' (i.e. free from water), especially in connexion with ester condensations requiring anhydrous ethanol. The sample is divided into two portions of about 20 ml. and placed in two stoppered cylinders; to one anhydrous baryta is added and the tube immediately stoppered and shaken. A solution containing barium ethoxide is obtained. When the supernatant liquid is clear a few drops is decanted into the untreated portion of the sample. The most minute trace of moisture will cause an opalescence due to decomposition of the barium ethoxide:—

$$Ba(OEt_2) + 2H_2O \longrightarrow Ba(OH)_2 + 2Et_2OH$$

Is this respect it is important from a practical point of view to note that the distillation or standing of alcohol over sodium does not remove the last traces of water, since the equilibrium

$$C_2H_5ONa + H_2O \rightleftharpoons C_2H_5OH + NaOH$$

lies appreciably on the left-hand side. On the other hand, metallic calcium or magnesium are suitable for drying alcohol, as they form at least one insoluble phase.

The chemical reactions of ethanol are typically those of a primary alcohol, and may be summarised in the following equations:—

$C_2H_5OH + HCl$	$\longrightarrow$	$C_2H_5Cl + H_2O$	Ethyl chloride
$C_2H_5OH + HBr$	$\longrightarrow$	$C_2H_5Br + H_2O$	Ethyl bromide
$C_2H_5OH + HI$	$\longrightarrow$	$C_2H_5I + H_2O$	Ethyl iodide
$C_2H_5OH + H_2SO_4$	$\longrightarrow$	$CH_3 . CH_2OSO_3H + C_2H_5OH \rightarrow (C_2H_5)_2SO_4$	Diethyl sulphate
	$\longrightarrow$	$CH_2{=}CH_2 \longleftarrow$	Ethylene
	$\longrightarrow$	$C_2H_5 . O . C_2H_5$	Diethyl ether
$C_2H_5OH + ClCOR$	$\longrightarrow$	C_2H_5OCOR	Ethyl esters
$2C_2H_5OH + O(COR)_2$	$\longrightarrow$	$2C_2H_5OCOR$	
$C_2H_5OH + HOOCR$	$\longrightarrow$	C_2H_5OCOR	
$C_2H_5OH + HNO_3$	$\longrightarrow$	$C_2H_5ONO_2$	Ethyl nitrate
$C_2H_5OH + HNO_2$	$\longrightarrow$	C_2H_5ONO	Ethyl nitrite
$C_2H_5OH + SO_3$	$\longrightarrow$	$HO . C_2H_4SO_3H$	Isethionic acid
	$\longrightarrow$	$HOSO_2{-}OCH_2 . CH_2SO_3H$	Ethionic acid
$C_2H_5OH + NaOH$	$\xrightarrow[500^\circ]{}$	$CH_3COONa + 2H_2$	Sodium acetate
$C_2H_5OH + P + I$	$\longrightarrow$	C_2H_6	Ethane
$2C_2H_5OH + O_2$	$\longrightarrow$	$2CH_3.CHO + 2H_2O$	Acetaldehyde
C_2H_5OH	$\xrightarrow[\text{oxidation}]{\text{fermentative}}$	CH_3COOH	Acetic acid

In most cases the implications and conditions of these reactions are discussed under the heading of the substances on the right-hand side of the arrow. There are, however, one or two reactions which, unlike those in the list above, are peculiar to ethyl alcohol ; one is its simultaneous chlorination and oxidation to chloral :—

$$C_2H_5OH \longrightarrow CCl_3CHO$$

which is used for the preparation of that material, although the Poulenc process in which ethanol is oxidised in the vapour phase to aldehyde and then chlorinated directly in the vapour phase to chloral, is more economical :—

$$C_2H_5OH \longrightarrow CH_3CHO + 3Cl_2 \longrightarrow CCl_3CHO + 3HCl$$

Another reaction peculiar to ethanol is the formation of fulminates with nitric acid and the nitrate of either mercury or silver (see Chap. IV., Vol. II). Under the influence of a condensed electrical discharge various products are obtained from ethanol, in which butadiyne, $CH{\equiv}C{-}C{\equiv}CH$, is the major constituent.

Propanol-1 (*n-Propyl alcohol*), was first discovered by Chancel[1] in brandy fusel-oil, and has since been shown to occur in most fusel oils, especially that from the products of fermentation of the nipa-palm.

Industrially *n*-propyl alcohol is a by-product of the Fischer-Tropsch synthesis of methanol :—

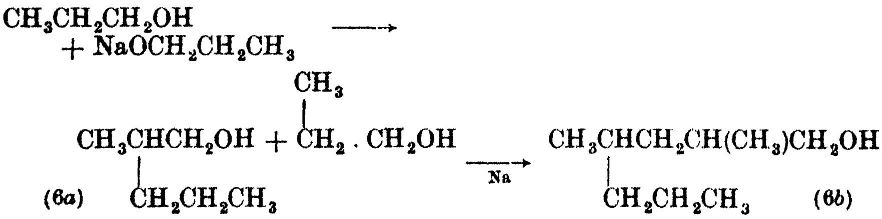
$$3CO + 6H_2 \longrightarrow C_3H_8O + 2H_2O$$

the mechanism is obscure, but the existing demand has been met from this by-product formation.

So far, none of the alternative syntheses devised from time to time have proved of industrial importance ; such syntheses have only a laboratory interest. They include :—

(*a*) The Grignard reaction from formaldehyde and ethyl magnesium bromide.
(*b*) The reduction of ethyl propionate.
(*c*) The conversion of natural propane to a mixture of 1- and 2- chlorides by direct chlorination, followed by saponification of the purified *n*-propyl chloride.
(*d*) The catalytic reduction of allyl alcohol, or of acrolein.

The reactions of propanol-1 are similar in nearly all respects to the general reactions of ethanol listed on page 267 ; in most respects it is slower to react. One of the characteristic reactions of propanol-1 is accomplished by heating it to 250° in an autoclave with an equimolecular proportion of sodium propoxide. The reaction takes place at the α-hydrogen atom, giving 2 methyl pentanol-1 (*6a*) :—



$$CH_3CH_2CH_2OH + NaOCH_2CH_2CH_3 \longrightarrow$$

$$\underset{(6a)\quad CH_2CH_2CH_3}{CH_3\underset{|}{C}HCH_2OH} + \overset{CH_3}{\overset{|}{C}}H_2 \cdot CH_2OH \xrightarrow[Na]{} \underset{CH_2CH_2CH_3\quad (6b)}{CH_3\underset{|}{C}HCH_2CH(CH_3)CH_2OH}$$

whilst by more drastic treatment the latter compound may be induced to react with a further molecule of propanol giving 2, 4-dimethylheptanol-1 (*6b*).

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[1] Chancel, *Ann.*, 1853, **87**, 127.

n-Butanol.—This alcohol was the last of the butyl alcohols to be discovered, being first prepared by Lieben and Rossi in 1869. It is now almost exclusively produced by the fermentation of maize-mash or molasses by the method introduced by Fernbach and Weizmann (see Appendix II). The yield is about 60 per cent. of the theoretical conversion, and there is about half this amount of acetone produced simultaneously. The separation of these is easy, and industrial butanol-1 is a fairly pure product. It is the first straight chain alcohol which is not completely miscible with water at ordinary temperatures. It is also prepared industrially by the catalytic reduction of crotonaldehyde :—

$$CH_3 . CH{=}CH . CHO \longrightarrow CH_3CH_2CH_2CH_2OH$$

n-Pentanol.—This is readily obtainable from pentane, which is fractionated from natural gas, chlorinated, and the product fractionated to give a tolerably pure 1-chloropentane. This, on hydrolysis, yields the alcohol. The other methods of synthesis discussed earlier under 'General Methods' are available.

Amongst the other *n*-alcohols, *n-hexyl alcohol* is prepared industrially by the condensation of butyraldehyde with acetaldehyde to give the unsaturated aldehyde (6*c*) which is reduced catalytically to hexanol-1 :—

$$CH_3CH_2CH_2CHO + CH_3CHO \longrightarrow \underset{(6c)}{CH_3CH_2CH_2CH{=}CH . CHO} \longrightarrow \underset{\text{Hexanol-1}}{CH_3(CH_2)_4CH_2OH}$$

n-Heptanol is derived almost exclusively from reduction of heptaldehyde from the destructive distillation of castor oil. An important member of the family of normal alcohols is *dodecanol-1* or lauryl alcohol, now available in ton quantities by the catalytic reduction of ethyl laurate from the lauric acid of coconut oil. This reaction is merely an extension of the reaction of Blanc and Bouveault (see p. 263). The crude product which contains some even numbered homologues of higher and lower carbon number, is capable of giving both dodecanol-1 and tetradecanol-1 on molecular distillation ; the mixture is known as 'Lorol', and is sulphated to give the so-called 'sulphonated Lorol', $CH_3(CH_2)_{10}CH_2OSO_3Na$, which is the sodium salt of lauryl sulphuric acid. These materials, which are entirely analogous to the soaps, are powerful surface tension reducers, and act, therefore, as detergents. The names 'Dreft' and 'Gardinol' are associated with such substances, and there is no doubt as to their superiority over soap for general detergent purposes, especially as their activity is undiminished in slightly acid water, sea-water and hard water, all of which are without effect on the washing power. The oxidation of higher petroleum fractions give acids which, when subjected to the same process, yield powerful detergents of this class—one example of such is 'Teepol'.

The normal straight chain primary alcohols are shown at the commencement of Table I, and it will be noted that the names carnaubyl, ceryl, melissyl, montanyl, gimnyl and the like are omitted, as the work of Chibnall (see 'Waxes', Appendix) has shown them not to be chemical individuals but to be complex mixtures. The names should not again be used, and in order to save confusion reference should be made to the systematic name of the individuals of the series.

Arborescent Primary Alcohols

Iso-butyl alcohol is the first primary alcohol with a branched chain ; and is the best known butyl alcohol, having been isolated from fusel oil by Wurtz. This is not a sufficient industrial source of the alcohol which is made in bulk by a modification of the Fischer-Tropsch synthesis using cobalt in the catalyst. This addition diverts more of the reactants towards the reaction :—

$$4CO + 8H_2 \longrightarrow (CH_3)_2CH . CH_2OH$$

TABLE I

PROPERTIES OF SOME ALCOHOLS (SATURATED)

Name	Formula	M.P.	B.P.	d.$_4^{\circ}$ except where stated	Remarks
Methanol	CH_3OH	−97·1°	64·65°	0·8100	Miscible with water.
Ethanol	CH_3CH_2OH	−114·15°	78·37°	0·80645	
Propanol-1	$CH_3CH_2CH_2OH$	−127° ?	97·4°	0·82135	
Butanol-1	$CH_3(CH_2)_2CH_2OH$	−79·9°	117·95°	0·2393	Soluble in 11 parts water at 15°
Pentanol-1	$CH_3(CH_2)_3CH_2OH$	—	137·5°	0·8296	Slightly soluble in water
Hexanol-1	$CH_3(CH_2)_4CH_2OH$	−90°	157°	0·8327	All subsequent alcohols are almost insoluble in water
Heptanol-1	$CH_3(CH_2)_5CH_2OH$	−35·5°	175·8°	0·8342	
Octanol-1	$CH_3(CH_2)_6CH_2OH$	−14°	193°	0·8375	
Nonanol-1	$CH_3(CH_2)_7CH_2OH$	−5°	213·5°	0·8415	
Decanol-1	$CH_3(CH_2)_8CH_2OH$	+ 7°	231°	0·8389$_7$	
Undecanol-1	$CH_3(CH_2)_9CH_2OH$	19°	135°/15 mm.	0·8334$_{23}$	
Dodecanol-1	$CH_3(CH_2)_{10}CH_2OH$	24°	143·5°/15 mm.	0·8309$_{24}$	Lauryl alcohol
Tridecanol-1	$CH_3(CH_2)_{11}CH_2OH$	30·5°	155·5°/15 mm.	0·8223$_{31}$	
Tetradecanol-1	$CH_3(CH_2)_{12}CH_2OH$	38°	167°/15 mm.	0·8236$_{38}$	
Pentadecanol-1	$CH_3(CH_2)_{13}CH_2OH$	46°	—	—	
Hexadecanol-1	$CH_3(CH_2)_{14}CH_2OH$	51°	189·5°/15 mm.	0·8105$_{60}$	Cetyl alcohol
Heptadecanol-1	$CH_3(CH_2)_{15}CH_2OH$	54°	—		
Octadecanol-1	$CH_3(CH_2)_{16}CH_2OH$	58·5	210°/15 mm.	0·8124$_{59}$	Stearyl alcohol
Nonadecanol-1	$CH_3(CH_2)_{17}CH_2OH$	65°	—		
Eicosanol-1	$CH_3(CH_2)_{18}CH_2OH$	71°	247° 8·5 mm.		
Docosanol-1	$CH_3(CH_2)_{20}CH_2OH$	74°	—		
Tetracosanol-1	$CH_3(CH_2)_{22}CH_2OH$	77°	—		
			Setting Point		
Hexacosanol-1	$CH_3(CH_2)_{24}CH_2OH$	79·5-8°	79·1°		The wax alcohols
Heptacosanol-1	$CH_3(CH_2)_{25}CH_2OH$	81·2-6°	81·0°		
Octacosanol-1	$CH_3(CH_2)_{26}CH_2OH$	83·2-4°	82·8°		
Nonacosanol-1	$CH_3(CH_2)_{27}CH_2OH$	84·6-85°	84·1°		
Triacontanol-1	$CH_3(CH_2)_{28}CH_2OH$	86·3-5°	85·9°		
Dotriacontanol-1	$CH_3(CH_2)_{30}CH_2OH$	89·3-5°	88·9°		
Tetratriacontanol-1	$CH_3(CH_2)_{32}CH_2OH$	91·9-92·2°	91·6°		
Hexatriacontanol-1	$CH_3(CH_2)_{34}CH_2OH$	93·2-6°	91·6°		

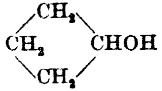
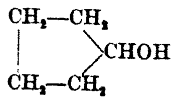
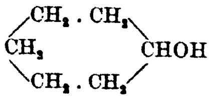
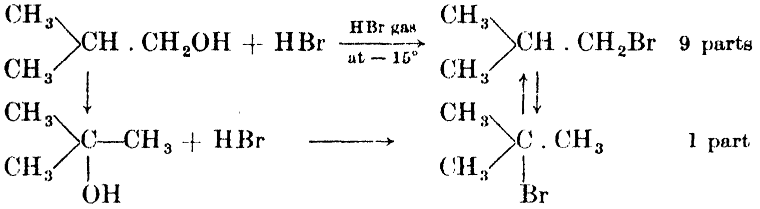
BRANCHED CHAINS			B P.	
Propanol-2	$(CH_3)_2CHOH$		82·4°	*iso*-Propyl alcohol
2-Methylpropanol-1	$(CH_3)_2CHCH_2OH$		108°	*iso*-Butyl alcohol
Butanol-2	$CH_3CH_2CHOH\ CH_3$		100°	*sec*-Butyl alcohol
***ter*-Butyl alcohol**	$(CH_3)_3C\ .\ OH$	25·5°	82·8°	
2-Methylbutanol-1	$CH_3CH_2CH(CH_3)CH_2OH$		128°	*sec*-Butyl carbinol
3-Methylbutanol-1	$(CH_3)_2CHCH_2CH_2OH$		131°	*iso*-Amyl alcohol
Pentanol-2	$CH_3CH_2CH_2CH(OH)CH_3$		119°	
Pentanol-3	$C_2H_5CH(OH)C_2H_5$		117°	Diethyl carbinol
2, 2-Dimethyl propanol	$(CH_3)_3C\ .\ CH_2OH$	54°	113°	
2-Methyl butanol-3	$(CH_3)_2CH\ .\ CH(OH)CH_3$		112°	*sec*-iso-Amyl alcohol
2-Methyl butanol-2	$CH_3CH_2C(OH)(CH_3)_2$		102°	*ter*-Amyl alcohol
(HEXYL ALCOHOLS. See special	Table (page 274)			
2, 4-Dimethyl pentanol-3	$(CH_3)_2CHCH(OH)CH(CH_3)_2$			
2, 3, 3-Trimethyl-butanol-2	$(CH_3)_3C\ .\ C(OH)(CH_3)_2$	17°	131°	
Octanol-2	$CH_3(CHOH)(CH_2)_5CH_3$		178°	Capryl alcohol
2-Ethylhexanol-1	$CH_3CH_2CH_2CH_2CH(Et)CH_2OH$			Available commercially
Allyl alcohol (propene-2-ol-1)	$CH_2{=}CH\ .\ CH_2OH$		96·5°	Completely miscible with water
Butene-1, ol-3	$CH_3CH(OH)CH{=}CH_2$		96°	
Butene-2, ol-1	$CH_3CH{=}CH\ .\ CH_2OH$		119°	Crotyl alcohol
Butene-1, ol-3	$CH_2{=}CH\ .\ CH(OH)CH_3$		96°	
Pentene-1, ol-3	$CH_2{=}CH\ .\ CH(OH)CH_2CH_3$		115°	
Pentene-2, ol-1	$CH_2OH\ .\ CH{=}CHCH_2CH_3$		139°	
Hexene-1, ol-3	$CH_2{=}CH\ .\ CH(OH)(CH_2)_2CH_3$		135°	
Hexene-2, ol-1	$CH_2OH\ .\ CH{=}CH(CH_2)_2CH_3$		159°	
4-Methyl pentene-1, ol-3	$CH_2{=}CH\ .\ CH(OH)\ .\ CH(CH_3)_2$		125°	
4-Methyl pentene-2, ol-1	$CH_2OH\ .\ CH{=}CH\ .\ CH(CH_3)_2$		150°	
Heptene-1, ol-3	$CH_2{=}CH\ .\ CH(OH)(CH_2)_3CH_3$		155°	
Heptene-2, ol-1	$CH_2OH\ .\ CH{=}CH(CH_2)_3CH_3$		178°	
Allyl carbinol	$CH_2{=}CH\ .\ CH_2CH_2OH$		113·5°	
Citronellol	$CH_2{=}C(CH_3)(CH_2)_3CH(CH_3)CH_2CH_2OH$		117-8/17 mm.	
Divinyl carbinol	$CH_2{=}CH\ .\ CH(OH)CH{=}CH_2$			Pentadiene 1-4, -ol-3
Propyn-ol	$CH\equiv C\ .\ CH_2OH$	— 17°	115°	Propargyl alcohol completely miscible with water
Butyn-1, ol-4	$CH\equiv C\ .\ CH_2\ .\ CH_2OH$			
Pentene-4, yn-1, ol-3	$CH_2{=}CH\ .\ CH(OH)\ .\ C\equiv CH$		decomp.	From acrolein with excess of Mg. acetylide
*cyclo*Butanol			123°	

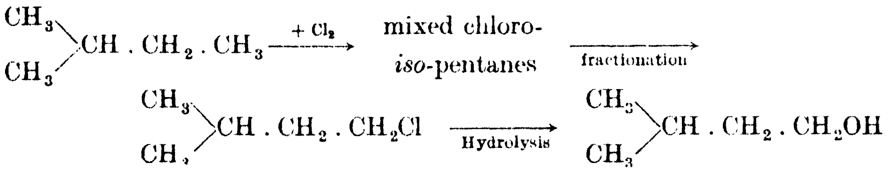
TABLE I (*continued*)

Name	Formula	M.P.	B.P.	d.$_4^{\circ}$ except where stated	Remarks
cycloPentanol			141°		
cycloHexanol		25°	161°		
cycloHeptanol			185°		
Menthols (see Chap. IX)					
Benzyl alcohol	$C_6H_5 . CH_2OH$		205°		
Phenyl ethyl alcohol	$C_6H_5 . CH_2CH_2OH$		221°		
Phenyl methyl carbinol	$C_6H_5 . CH(OH)CH_3$		204°		
Diphenyl carbinol	$(C_6H_5)_2CHOH$	69°	298°		Benzhydrol
Triphenyl carbinol	$(C_6H_5)_3COH$				
Cinnamyl alcohol	$C_6H_5CH{=}CH . CH_2OH$	33°	265°		
β-Phenyl propargyl alcohol	$C_6H_5C{\equiv}C . CH_2OH$		136°/13 mm.		

The reactions of *iso*-butanol are not widely different from those of the normal primary alcohols, except that rearrangements occur ; thus during esterification with mineral acids, e.g. HCl or HBr, considerable amounts of the tertiary butyl compounds make their appearance owing to an isomeric change :—

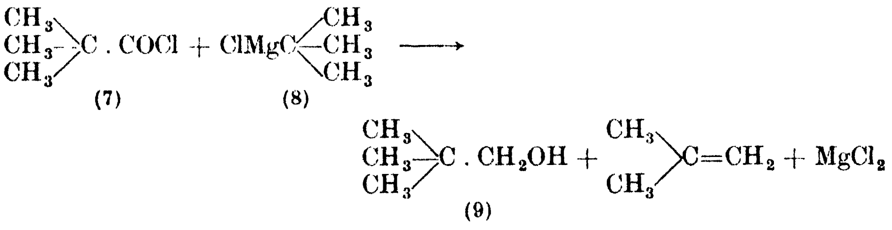


Iso-amyl Alcohol.—Although this alcohol was originally found in fusel oil, and was extracted from it by fractional distillation for industrial purposes, the supply could not keep up with the demand, and it is now manufactured in bulk from the *iso*-pentane available from the petroleum industry. The procedure is as follows :—



There is also a second primary alcohol of the amyl series, namely, 2, 2-dimethyl propanol-1, or '*neo*pentyl alcohol' (9). Direct methods of obtaining this alcohol from *iso*pentane are difficult to achieve, and in preparing *neo*pentyl alcohol the following methods are used :—

(1) Trimethyl acetyl chloride (7) is treated with the Grignard reagent from *ter*-butyl chloride (8) :—



This reaction is unusual in its course, but is nevertheless probably the simplest way of making *neo*-pentyl alcohol in the laboratory ; industrially it can be prepared by the hydrolysis of *neo*-pentyl chloride.

The reactions of *neo*-pentyl alcohol are anomalous and lead to tertiary-derivatives almost exclusively, or, in the case of halide acids, lead to *ter*-amyl derivatives and trimethylethylene :—

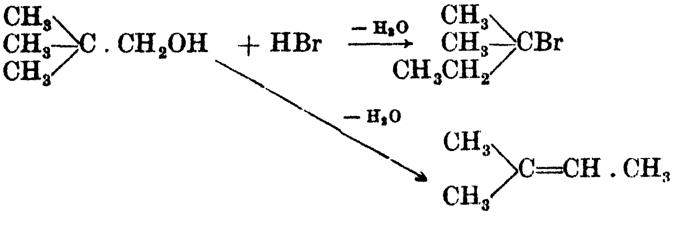


TABLE II

THE SEVENTEEN HEXYL ALCOHOLS

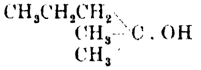
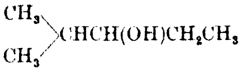
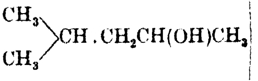
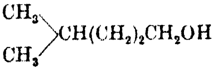
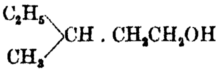
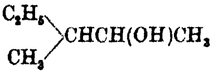
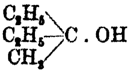
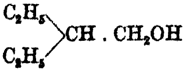
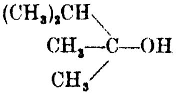
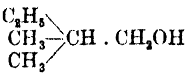
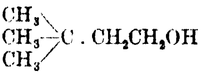
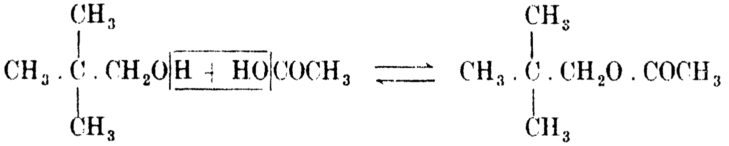
No.	Name	Formula	Physical Properties	Mode of preparation, etc.
1	Hexanol-1	$CH_3(CH_2)_4CH_2OH$	b. 157°	(See p. 269)
2	Hexanol-2	$CH_3CH(OH)(CH_2)_3CH_3$	b. 141°	(*a*) From hexene-1 by shaking with H_2SO_4, diluting and distillation (*b*) Reduction of hexanone-2
3	Hexanol-3	$C_2H_5 . CH(OH)C_3H_7$	b. 135°	(*a*) Ethyl magnesium bromide and *n*-butyraldehyde (*b*) From ethyl propyl ketone, by reduction
4	2-Methylpentanol-1	$CH_3(CH_2)_2CH(CH_3)CH_2OH$	b. 147°	A by-product in the Fischer-Tropsch synthesis of methanol from $CO + H_2$ (2) Guerbert's reaction (see under 'Propyl alcohol', p. 268)
5	2-Methylpentanol-2	 $\begin{matrix} CH_3CH_2CH_2 \diagdown & \\ CH_3 - & C . OH \\ CH_3 \diagup & \end{matrix}$	b. 123°	(*a*) From methyl magnesium bromide and ethyl-*n*-butyrate (*b*) From acetone and *n*-propyl magnesium bromide
6	2-Methylpentanol-3	 $\begin{matrix} CH_3 \diagdown & \\ & CHCH(OH)CH_2CH_3 \\ CH_3 \diagup & \end{matrix}$	b. 128°	(*a*) From isobutyraldehyde and ethyl magnesium bromide. The alcohol has been resolved *via* the strychnine salt of the ½ phthalic ester $[\alpha]_D^{21} = + 12{\cdot}4°$
7	2-Methylpentanol-4	 $\begin{matrix} CH_3 \diagdown & \\ & CH . CH_2CH(OH)CH_3 \\ CH_3 \diagup & \end{matrix}$	b. 132°	Made industrially from the catalytic dehydration and hydrogenation of diacetone alcohol. Resolved *via* the brucine salt of the ½ phthalic ester $[\alpha]_D^{20} = + 20{\cdot}4°$
8	2-Methylpentanol-5 (4-Methylpentanol-1) Isohexyl alcohol	 $\begin{matrix} CH_3 \diagdown & \\ & CH(CH_2)_2CH_2OH \\ CH_3 \diagup & \end{matrix}$	b. 148°	(*a*) From paraform and *iso*amyl magnesium bromide (*b*) From ethylene oxide + *iso*butyl magnesium bromide (*c*) From *iso*butylacetoacetic ester
9	3-Methyl-pentanol-1	 $\begin{matrix} C_2H_5 \diagdown & \\ & CH . CH_2CH_2OH \\ CH_3 \diagup & \end{matrix}$	b. 153°	Occurs in Roman chamomile. Synthesised from *sec*-butyl carbinol *via* bromide and Grignard, reacting with paraform
10	3-Methyl-pentanol-2	 $\begin{matrix} C_2H_5 \diagdown & \\ & CHCH(OH)CH_3 \\ CH_3 \diagup & \end{matrix}$	b. 134°	From methyl ethyl acetoacetic ester *via* methyl *sec*-butyl ketone by sodium and moist ether
11	3-Methyl-pentanol-3 Methyldiethyl carbinol	 $\begin{matrix} C_2H_5 \diagdown & \\ C_2H_5 - & C . OH \\ CH_3 \diagup & \end{matrix}$	b. 123°	From ethyl acetate + excess Mg ethyl bromide (cf. synthesis of terpineol)
12	2-Ethylbutanol-1	 $\begin{matrix} C_2H_5 \diagdown & \\ & CH . CH_2OH \\ C_2H_5 \diagup & \end{matrix}$	b. 146°	By an aldol condensation between acetaldehyde and *n*-butyraldehyde and reduction. By catalytic reduction of diethylacetic ester

TABLE II (*continued*)

No.	Name	Formula	Physical Properties	Mode of preparation, etc.
13	2, 3-Dimethyl-butanol-1	$(CH_3)_2CH.CH(CH_3)CH_2OH$	b. 145°	Very difficult to prepare; best made by reducing Me *iso*propyl acetic ester with sodium and alcohol
14	2, 3 Dimethyl-butanol-2	 $(CH_3)_2CH(CH_3)_2C{-}OH$	b. 118-122°	Grignard reaction from trimethylene oxide and methyl magnesium bromide. Or *iso*butyric methyl ester with excess MeMgBr
15	2, 2-Dimethyl-butanol-1 *ter*-Amyl carbinol	 $C_2H_5(CH_3)_2C.CH_2OH$	b. 135°	From *ter*-amyl magnesium bromide and paraform, or methyl formate
16	3, 3-Dimethyl-butanol-2 Pinacolyl alcohol	$(CH_3)_3C.CH(OH)CH_3$	m. 6°; b. 121° $[\alpha]_D^{20} = +7{\cdot}7°$	Reduction of pinacolone, from pinacol
17	3, 3-Dimethyl-butanol-1	 $(CH_3)_3C.CH_2CH_2OH$	b. 143°	*neo*Pentyl carbinol (for its preparation see p. 280)

There is one striking exception to this rearrangement, namely, the ease with which *neo*pentyl alcohol is converted to its esters and these reconverted to the alcohol in almost theoretical yield :—



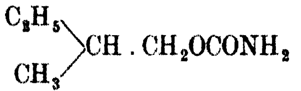
$$CH_3.\underset{CH_3}{\overset{CH_3}{C}}.CH_2O\boxed{H + HO}COCH_3 \rightleftharpoons CH_3.\underset{CH_3}{\overset{CH_3}{C}}.CH_2O.COCH_3$$

This, in view of the extensive rearrangements which take place when the hydroxyl group is removed from *neo*pentyl alcohol, has been taken as confirmation that in esterification it is the alcohol that contributes the H, and the acid the —OH.

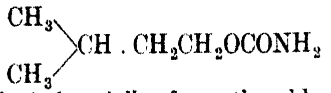
The third primary amyl alcohol is 2-methyl butanol-1,

$$CH_3CH_2(CH_3)CHCH_2OH,$$

a minor constituent of fusel oil, and often referred to as 'active' amyl alcohol, since its asymmetric molecule leads to optical activity. It was, at one time, separated from fusel oil by treating the amyl alcohol fraction with sulphuric acid and crystallising the barium salts of the amyl sulphates so obtained. Repeated fractional crystallisation effects a separation of the isomers. Recently a more rapid separation has been achieved by treating the mixed alcohols with 'urea chloride' (carbamic chloride) and fractionally crystallising the carbamates :—



$$\begin{matrix}C_2H_5\\CH_3\end{matrix}\!\!>CH.CH_2OCONH_2$$



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH.CH_2CH_2OCONH_2$$

Since 1-chloro-2-methylbutane is available industrially from the chlorination of *iso*pentane, it will serve as source of racemic 'active' amyl alcohol, when required.

SECONDARY ALCOHOLS

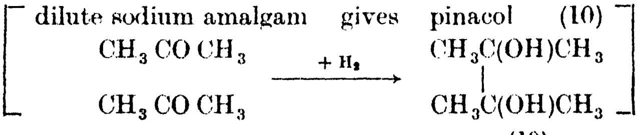
Propanol-2 (*Iso*-propyl alcohol) $(CH_3)_2CHOH$. This alcohol was first prepared by Berthelot[1] in 1855 by absorbing propylene in sulphuric acid, diluting the liquor with water and distilling. Unfortunately he made his experiments before the recognition of isomerism in the alcohol series, and it was assumed for years that the alcohol prepared in this way was identical with that from fusel oil. It is interesting to note that it is precisely by this reaction that train-loads of propanol-2 are prepared to-day from the propylene obtained as a by-product of the petroleum industry. The sulphuric acid *absorbate*, when saturated with propylene, can be treated to give di-*iso*-propyl ether

$$(CH_3)_2CH\ .\ O\ .\ CH(CH_3)_2$$

which is thereby obtained in large yield and at a low price. It is an excellent solvent, but its applications are, to some extent, limited by its tendency to form explosive peroxides.

Friedel[2] obtained *iso*propyl alcohol by the strenuous reduction of acetone with sodium :—

$$CH_3COCH_3 \xrightarrow[H_2]{} CH_3CH(OH)CH_3$$

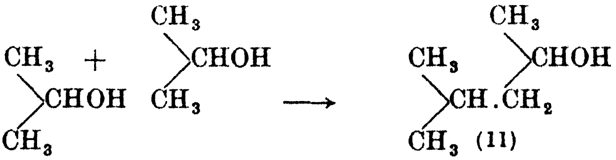


$$\left[\begin{array}{ccc} \text{dilute sodium amalgam} & \text{gives} & \text{pinacol (10)} \\ \begin{matrix} CH_3\,CO\,CH_3 \\ CH_3\,CO\,CH_3 \end{matrix} & \xrightarrow{+H_2} & \begin{matrix} CH_3C(OH)CH_3 \\ | \\ CH_3C(OH)CH_3 \end{matrix} \end{array}\right]$$

(10)

and Kolbe[3] pointed out that this must be the secondary alcohol, the existence of which he had predicted.

Prior to the use of propylene as a raw material, *iso*-propyl alcohol was manufactured by the reduction of acetone by Friedel's method, and now a curious *volte-face* has been made in industry, since a fair amount of acetone is manufactured in the U.S.A. by catalytic oxidation of *iso*-propanol. During the formation of *iso*-propyl alcohol from propylene none of its normal isomer is formed, although 4-5 lb. per ton of methyl*iso*butyl carbinol (11) are formed :—



This reaction is merely a modification of Guerbert's synthesis, which proceeds very well with *iso*-propanol and sodium *iso*propoxide. The process is used in the U.S.A. for manufacturing 4-methyl pentanol-2 (called, in industry, di-*iso*propyl alcohol).

iso-Propyl alcohol is a substance which rapidly attained industrial importance as a solvent; although it is not possible to use it for beverage purposes, it can still be used in essences, and for medicinal solutions for external application.

In most properties *iso*-propanol resembles the primary alcohols; it forms an azeotrope with 12 per cent. of water. The formation of esters from *iso*-propanol, although proceeding normally, is more difficult to bring about on account, probably, of the steric factor; it takes place more slowly and requires more active reagents; the same degree of inhibition is to be observed in the formation of alkoxides from *iso*propanol. On the other hand, as with the majority of secondary alcohols, it is easier to split off water and form the unsaturated hydrocarbon than with the corresponding primary alcohols.

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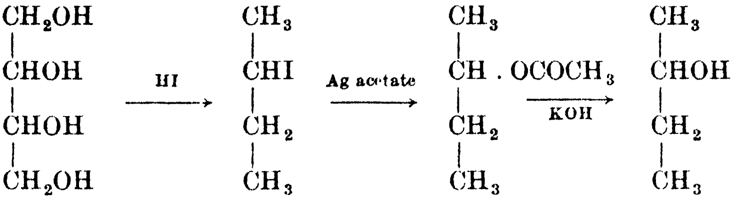
[1] Berthelot, *Ann. Chim. Phys.*, 1855, (3), **43**, 399.

[2] Friedel, *Ann.*, 1862, **124**, 324.

[3] Kolbe, *Zeitschr. Chem.*, 1866, 118.

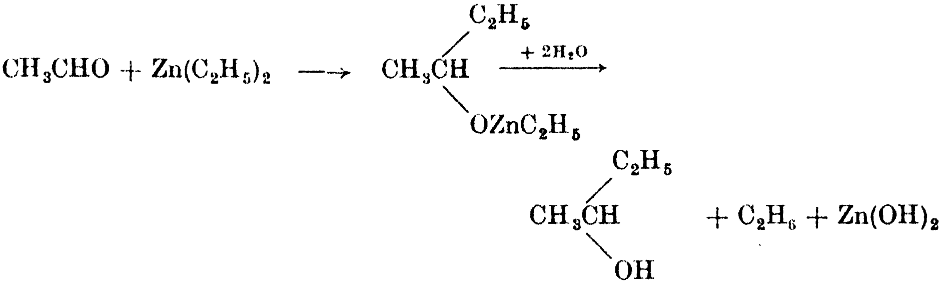
The main difference between *iso*propanol and its normal isomer, lies in its oxidation to acetone, sufficiently familiar not to need further comment.

sec-Butanol.—De Luynes [1] prepared this alcohol in 1864, from erythrite by the following steps :—



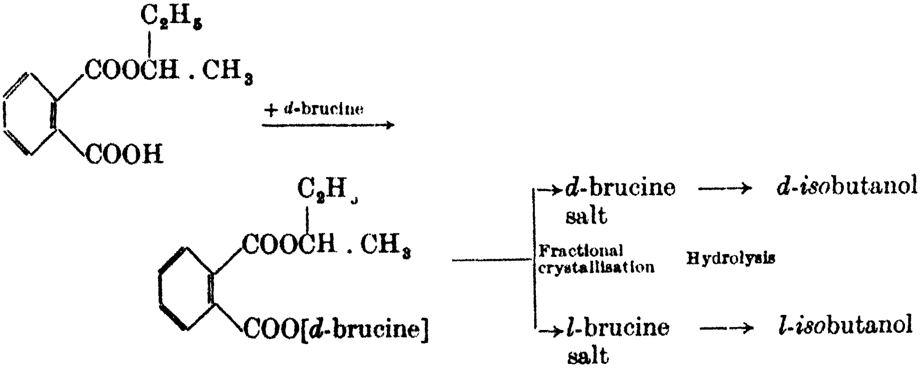
$$CH_2OH\cdot CHOH\cdot CHOH\cdot CH_2OH \xrightarrow{HI} CH_3\cdot CHI\cdot CH_2\cdot CH_3 \xrightarrow{\text{Ag acetate}} CH_3\cdot CH.OCOCH_3\cdot CH_2\cdot CH_3 \xrightarrow[KOH]{} CH_3\cdot CHOH\cdot CH_2\cdot CH_3$$

A second synthesis, of Kanovnikov and Sätzov,[2] consists in heating equimolecular proportions of ethyl formate and methyl and ethyl iodides with zinc-sodium alloy. It may also be obtained from anhydrous aldehyde and zinc diethyl, followed by hydrolysis with water :—



Ethyl magnesium iodide can replace the zinc dialkyl. Industrially, an ample supply of butanol-2 is available by the absorption of butylene from cracker gas in sulphuric acid followed by dilution and distillation.

sec-Butanol is the simplest alcohol capable of being resolved into optical isomers. The method of Pickard and Kenyon is so widely used as to warrant description here. The racemic alcohol is allowed to react with phthalic anhydride when a half ester is formed. This is capable of forming a mixture of salts with *d*-brucine, which are no longer enantiomorphous, and can be separated by fractional crystallisation :—



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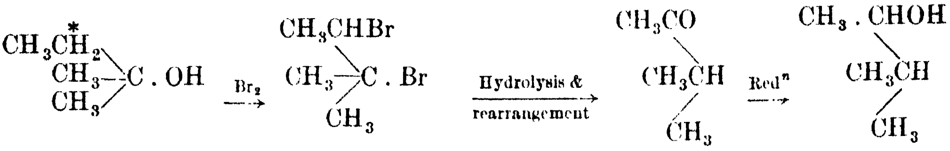
[1] De Luynes, *Ann. Chim. Phys.*, 1864, (4) **2**, 385.

[2] Kanovnikov and Sätzov, *Ann.*, 1875, **175**, 374.

The Secondary Amyl Alcohols

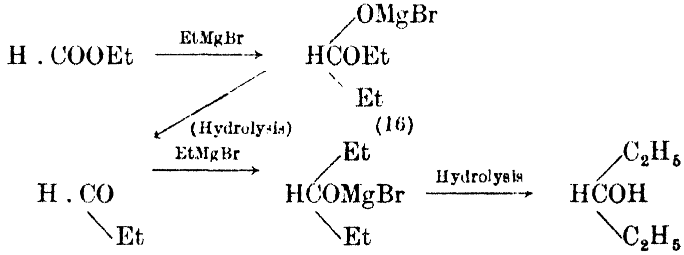
sec- iso-Amyl alcohol (2-methylbutanol-3) b. 112° is a difficult material to obtain by direct substitution, and the easiest way to obtain it is to commence



(12) (13) (14)

with *ter*-amyl alcohol (12); when this is brominated, the halogen enters the position marked (*) and the liberated hydrogen bromide esterifies the hydroxyl group, giving 2-methyl 2, 3-dibromobutane (13). This, on treatment with alkali yields, by hydrolysis and rearrangement, a ketone reducible to the desired alcohol (14). The alcohol is an excellent source of methyl *iso*-propyl ketone which is obtained from it by oxidation.

Pentanol-3, often called diethyl carbinol $(C_2H_5)_2CHOH$, was formerly prepared by the Grignard method, using ethyl formate and excess of magnesium ethyl bromide :—



(15) (16)

The intermediate stage, propionaldehyde (15) can, if available, be used as a starting point. It should, however, be pointed out that there is no necessity to observe the stages set out in the formulæ above ; the intermediate (16) is so unstable that it breaks down spontaneously to propionaldehyde, so that by treating ethyl formate with rather more than twice its equivalent of ethyl magnesium bromide the product isolated on treatment with acid is pentanol-3.

Industrially, an ample supply of pentanol-3 can be obtained from 3-chloropentane, a fraction from the chlorination of pentane.

Pentanol-2 (methyl propyl carbinol), $CH_3CH_2CH_2CH(OH)CH_3$, can be obtained in a variety of ways ; the reduction of the appropriate ketone and the various systematic Grignard syntheses all proceed normally. Industrially, there is a choice of methods for production of this alcohol, either from pentene-2 by hydration with sulphuric acid in the usual way, or from the 2-chloropentane, which is readily available from the chlorination of pentane. Industrial *sec*-amyl alcohol usually contains about 80 per cent. of pentanol-2 and 20 per cent. pentanol-3.

Tertiary Alcohols

ter-Butyl alcohol (2-methyl propanol-2) is the simplest tertiary alcohol. Discovered by Butlerov,[1] in 1863, by decomposing the product of the interaction of phosgene and zinc dimethyl with water (16*a*).

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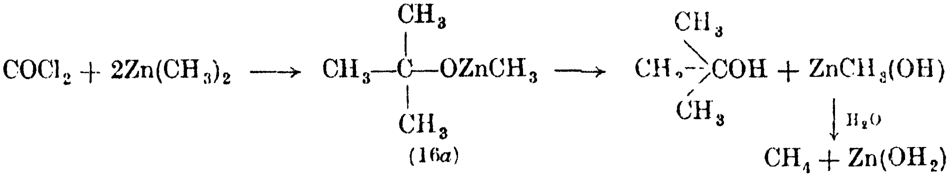
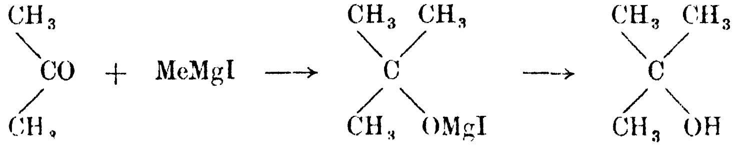
[1] Butlerov, *Zeits. Chem.*, 1863, 484.

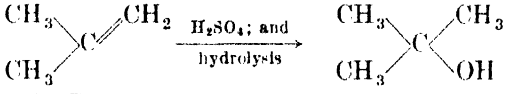


(16a)

Needless to say, this most inconvenient preparation was soon replaced by more convenient methods, of which the action of magnesium methyl iodide on acetone is one :—



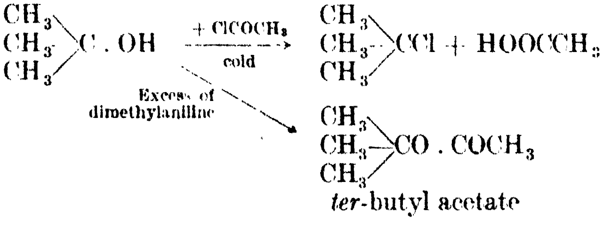
It is made industrially as a by-product in the manufacture of *sec*-butyl alcohol. This latter substance is manufactured from butylene ; the industrial butylene contains some *iso*butylene, which has to be scrubbed out by a more dilute sulphuric acid than that used for the absorption of the butylene itself ; it is the first absorption liquor that, on dilution and distillation, yields the *ter*-butyl alcohol.



iso-Butylene *ter*-Butanol

The accumulation of three alkyl groups on a single carbon atom to which a hydroxyl group is attached, leads to a comparatively unstable molecule, and imparts new properties to the tertiary alcohols which are not encountered in their primary and secondary isomers. Thus, the lability of the hydroxyl is such that it is completely replaced by chlorine on shaking with concentrated hydrochloric acid at room temperature ; removal of the acid layer, washing and rectification of the *ter*-butyl chloride is all that is required to obtain the pure halide.

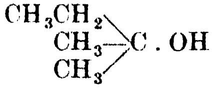
Again, *ter*-butyl alcohol is dehydrated when warmed with dilute inorganic acids, giving *iso*-butylene. *ter*-Butyl alcohol is only very slowly esterified and must, therefore, be removed from mixed butanol fractions to be used for solvent ester manufacture. Butlerov described in his early investigations a reaction which is one of the more striking examples of the lability of the hydroxyl group in tertiary alcohols, namely, that on mixing equimolar quantities of acetyl chloride and *ter*-butyl alcohol a quantitative double decomposition is attained :—



ter-butyl acetate

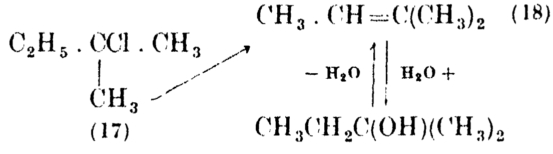
In the presence of dimethyl aniline the acetate is formed. As there is no possibility of a direct oxidation of *ter*-butyl alcohol to an aldehyde or ketone, as with primary and secondary alcohols, fairly vigorous measures are necessary to achieve oxidation. The products are acetone, carbon dioxide, acetic acid and some *iso*butyric acid $(CH_3)_2CHCOOH$.

ter-Amyl Alcohol.



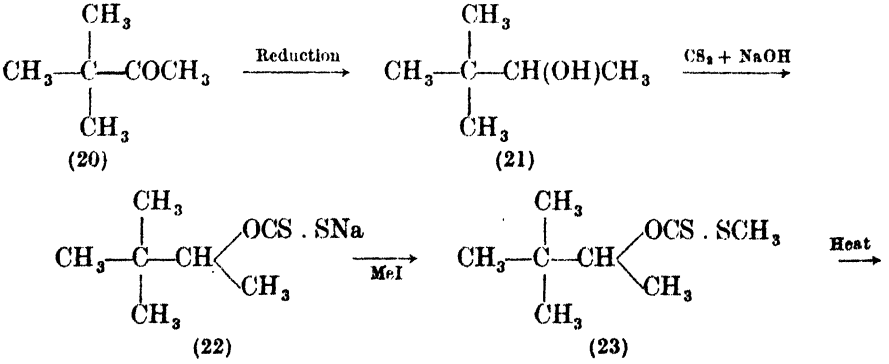
$$CH_3CH_2(CH_3)_2C.OH$$

Popov's original method[1] of treating propionyl chloride with zinc dimethyl has long been replaced by more convenient processes for preparing *ter*-amyl alcohol. The Grignard method could, if necessary, be used, and has been applied to obtain pure substances for characterisation. Fortunately, ample supplies of this material are available from the appropriate chloropentane. In practice the chlorination of pentane and *iso*-pentane are not, primarily, conducted for the purpose of obtaining *ter*-amyl alcohol; but during the chlorination some 2-chloro *iso*-pentane (17) is inevitably formed. During the subsequent treatment of the mixed halides to produce the amyl alcohols any 2-chloro-*iso*-pentane present is converted into *tri*-methylethylene (18), which, on account of its low b.p. (38·4°) distils out alone. If it is allowed to stand with the stoichiometric amount of water, it forms "amylene hydrate" or *ter*-amyl alcohol (19). This reaction between *tri*-methylethylene and water may be demonstrated by sealing a little *ter*-amyl alcohol in a stout-walled tube with some dilute sulphuric acid; on standing in hot water, the liquid separates in two layers, one of amylene, and one of dilute acid; on cooling they coalesce. In this and other respects the properties of *ter*-amyl alcohol resemble very closely those already described in connexion with *ter*-butyl alcohol. It is used in the dry cleaning trade, for cleaning 'Celanese' by immersion, and is used as a 'spotting liquid', i.e. to remove the spots (usually grease or sugar) from garments prior to dry cleaning with the more usual chlorinated solvents.



HIGHER ALCOHOLS

The hexyl family is the last group of alcohols of which all the possible isomers are known. They are listed with their boiling points and methods of preparation in Table II. One method of preparation is so long that it has been omitted from the Table, and is given below. It is the preparation of the most difficultly obtainable of the hexyl group—3, 3-dimethyl butanol-1, or *neo*-pentyl carbinol. The starting point may be conveniently taken as pina-


$CH_3C(CH_3)_2COCH_3$
(20)
Reduction
$CH_3C(CH_3)_2CH(OH)CH_3$
(21)
$CS_2 + NaOH$
$CH_3C(CH_3)_2CH(CH_3)OCS.SNa$
(22)
MeI
$CH_3C(CH_3)_2CH(CH_3)OCS.SCH_3$
(23)
Heat

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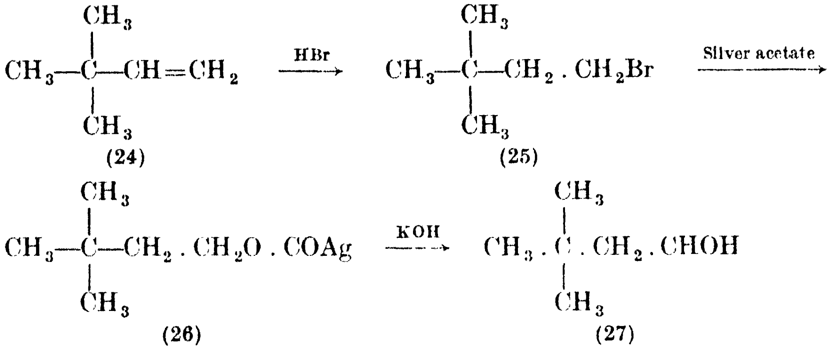
[1] Popov, **Ann.**, **1868, 145, 292.**



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH=CH_2 \xrightarrow{HBr} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2.CH_2Br \xrightarrow{\text{Silver acetate}}$$

(24) (25)

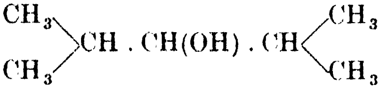
$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2.CH_2O.COAg \xrightarrow{KOH} CH_3.\overset{CH_3}{\underset{CH_3}{C}}.CH_2.CHOH$$

(26) (27)

cone (20), which can be reduced to pinacolyl alcohol (21) and converted to the xanthate (22). On methylating the latter (23) and heating the methyl derivative, *ter*-butyl-ethylene is obtained (24), which adds on hydrobromic acid contrary to Markownikov's rule (25); probably owing to the steric factor of the *ter*-butyl group. The bromide can be converted to the alcohol (27) *via* the acetate (26).

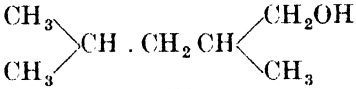
Of the thirty-nine heptyl alcohols theoretically possible, about fifteen are known, and of the eighty-nine octyl alcohols twenty-six are known. The following members of the group are available in quantity :—

(1) 2, 4-Dimethyl pentanol-3, called di-*iso*propyl carbinol (28) formed in



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>CH.CH(OH).CH<\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

(28)



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>CH.CH_2CH<\!\begin{matrix}CH_2OH\\CH_3\end{matrix}$$

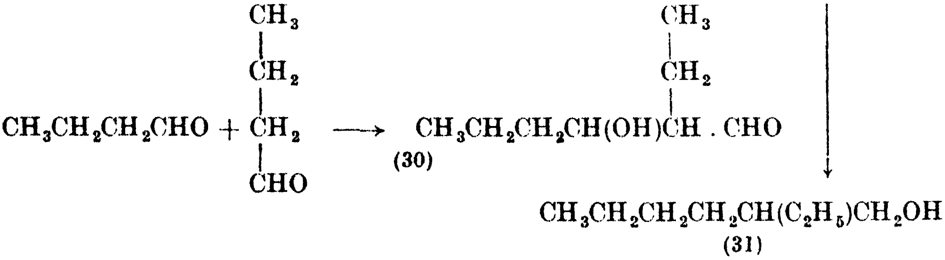
(29)

the Fischer-Tropsch synthesis; it is the main secondary alcohol formed, and is accompanied by smaller quantities of 2, 4-dimethyl pentanol-1 (29).

Apart from the octyl alcohol (32), which has for a long time been available

$$CH_3CH_2CH_2CH_2CH_2CH_2CHOHCH_3 \quad (32)$$

from the destructive distillation of castor oil, the only octyl alcohol available in any quantity is 2-ethyl hexanol-1. This is obtained by an aldol condensation between two molecules of *n*-butyraldehyde, giving the product (30) which



$$CH_3CH_2CH_2CHO + \begin{matrix}CH_3\\|\\CH_2\\|\\CH_2\\|\\CHO\end{matrix} \longrightarrow CH_3CH_2CH_2CH(OH)\overset{\overset{CH_3}{|}}{\overset{CH_2}{\overset{|}{C}}}H.CHO \longrightarrow CH_3CH_2CH_2CH_2CH(C_2H_5)CH_2OH$$

(30) (31)

is then dehydrated and reduced to the alcohol (31). Even-numbered alcohols from C_{10}—C_{18} are articles of commerce, and a number of the higher alcohols have been synthesised by Chibnall, Piper and others in connexion with their studies on waxes (*q.v.*).

UNSATURATED ALCOHOLS

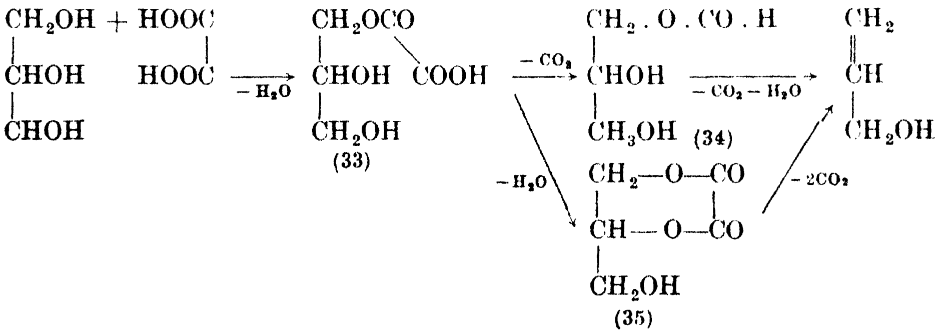
The simplest unsaturated alcohol should be vinyl alcohol, but this is the enolic form of acetaldehyde :—

$$CH_3CHO \rightleftharpoons CH_2=CH.OH$$

and it is a general rule that simple substances exist in the keto form almost entirely. The equilibrium that exists between such types is more apparent in substances such as acetoacetic ester (*q.v.*) in which the enol and keto forms exist side by side and may be separated, whilst where the molecular weight of a β-ketonic ester is higher the two forms are even more stable. The phenomena associated with this equilibrium are referred to as 'tautomerism', and are dealt with at length in Chapter IV, Vol. III. The $-C(OH)=C-$ structure can be stabilised by esterifying or etherifying the hydroxyl group, thus divinyl ether (*q.v.*), $CH_2=CH.O.CH=CH_2$, and vinyl ethyl ether, $CH_2=CH.OC_2H_5$, are stable substances; whilst vinyl acetate, $CH_2=CH.OCOCH_3$, is an important industrial chemical in the plastics field.

Allyl alcohol, $CH_2=CH.CH_2OH$. In 1844 Wertheim[1] isolated from garlic (*Allium sativum*) an oil which he recognised as the sulphide of a new radicle, C_3H_5; he called this radicle 'allyl', and twelve years later Hofmann and Cahours[2] first obtained the alcohol by treating the iodide (previously prepared by Berthelot from glycerol, phosphorus and iodine) with silver oxalate to obtain allyl oxalate, and passing a current of ammonia through the oxalate; oxamide separated and the allyl alcohol was distilled from a calcium chloride bath. The alcohol occurs in the neutral liquor separating from the liquid portion of the wood distillation products, and may be distilled out by taking advantage of the extremely low boiling azeotrope with 27·7 per cent. of water, which boils at 87·5°, and may be distilled out of the liquid. Potassium carbonate added to the distillate salts out the alcohol itself, which may be rectified over baryta. The product contains a little propanol.

The usual method for its synthetic preparation is the distillation of glycerol with anhydrous oxalic acid; if the oxalic acid is a 'commercial' grade, containing small quantities of oxalates, a little ammonium chloride is added to neutralise the effect of these salts which is to diminish the yield of allyl alcohol. The reaction appears to follow the course shown below, in which the mono acid oxalate of glycerol (33) is first formed; it is customary to state that the next step is the loss of carbon dioxide to give monoformin (34); but Chattaway has shown that the major portion, at least, of the reaction goes through the neutral oxalic ester (35) which loses two molecules of carbon dioxide to form allyl alcohol. A little allyl formate distils with the alcohol and water.



Allyl alcohol is a colourless liquid, with a pungent smell, which as a general rule is due less to the substance itself than to traces of allyl formate. Chemically, allyl alcohol is reactive; on pyrolysis it gives acrolein, which substance is also readily obtained when allyl alcohol is submitted to aerial oxidation in the presence of platinum. It can be reduced to propanol; hypochlorous acid adds to allyl alcohol to give the symmetrical chlorohydrin of glycerol contrary to the prediction of the Markownikov rule. In general, therefore, it may be said that allyl alcohol normally fulfils its dual rôle of alcohol and unsaturated hydrocarbon. It has been proposed to use the ozonide of this alcohol to make glyoxal, which it gives on hydrolysis.

---

[1] Wertheim, *Ann.*, 1844, **51**, 289.

[2] Hofmann and Cahours, *ibid.*, 1856, **100**, 355; 1857, **102**, 285.

Methyl vinyl carbinol, $CH_3 . CHOH . CH{=}CH_2$. This alcohol, which is representative of the alkyl vinyl carbinols, is obtained by the Grignard method, from methyl magnesium bromide and acrolein. The solutions must be well refrigerated. The reaction takes the normal course. The vinyl carbinols

$$CH_2{=}CH . CHO \xrightarrow[CH_3MgBr]{} CH_2{=}CH . CH(OH)CH_3$$

dehydrate normally as secondary alcohols, giving, in the case of methyl vinyl carbinol, butadiene ; by the use of the higher alkyl vinyl carbinols we have almost the only convenient approach to the alkyl butadienes ; the field has been carefully investigated by Bouis.[1]

Crotyl alcohol, $CH_3 . CH{=}CH . CH_2OH$. The reduction of crotonaldehyde to the alcohol has proved a difficult task, and extremely poor yields of impure material was obtained until aluminium *iso*propoxide was used as the reducing agent. The use of aluminium ethoxide and other alkoxides for the reduction of unsaturated alcohols to aldehydes is a very valuable reaction, as in the majority of cases the remainder of the molecule is entirely undisturbed.[2] In principle, the reaction takes the following course :—

$$3RCHO + Al(OEt)_3 \longrightarrow 3CH_3CHO + Al(OR)_3$$

the volatile aldehyde being distilled off ; with aluminium *iso*-propoxide, acetone is produced. The method has been widely applied in the vitamin A field (see Chap. XI). The alternative method for the preparation of crotyl alcohol is to commence with methyl vinyl carbinol, which on treatment with phosphorus tribromide gives crotyl bromide, by rearrangement. This, on warming with acetic acid and sodium acetate, gives crotyl acetate which may be saponified by a slight excess of cold aqueous sodium hydroxide :—

$$CH_3CHOH . CH{=}CH_2 \xrightarrow{HBr} CH_3CH{=}CHCH_2Br \xrightarrow{Ac_2O + NaOAc}$$
$$CH_3CH{=}CHCH_2O . COCH_3 \xrightarrow{dil\ NaOH} CH_3CH{=}CH . CH_2OH$$

Crotyl alcohol is a liquid which behaves as a normal unsaturated primary alcohol.

Amongst the higher unsaturated alcohols are phytol, and the terpene alcohols nerol, linalöol and citronellol ; these are discussed in Chapters VIII and XI.

ACETYLENIC ALCOHOLS

Although the acetylenic alcohols are not, of themselves, of great importance, they act as most valuable links in the synthesis of various less unsaturated alcohols. The reaction of Moureu consists in condensing the sodium salt of an acetylene with an aldehyde :—

$$R . C{\equiv}C . Na + R'CHO \longrightarrow R{-}C{\equiv}C . CH(ONa)R'$$

There are two important modifications of this method, namely, the use of the magnesium acetylene halide :—

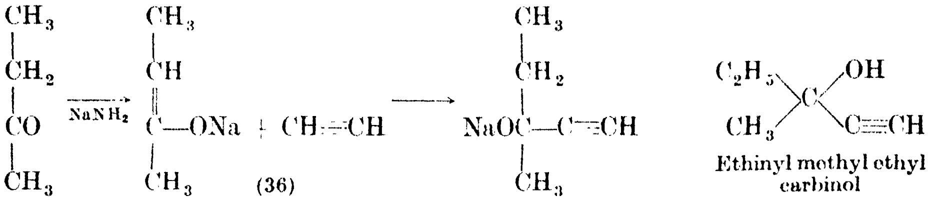
$$R . C{\equiv}C . MgBr + CH_3CHO \longrightarrow R . C{\equiv}C . CH(OH)CH_3$$

and the action of acetylene in the presence of sodamide on a ketone. This latter reaction is probably the most important of all, in that it is capable of very wide application, with easily accessible reagents. The function of the sodamide is to induce the formation of the sodio-enol derivative of the ketone (36), which then reacts as follows :—

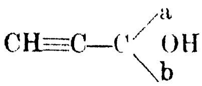
---

[1] Bouis, *Ann. Chem.*, 1928, **9**, 427 and 430.

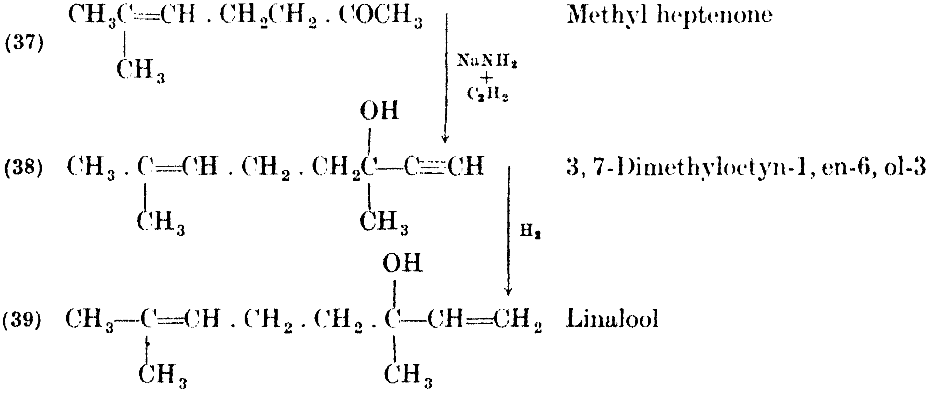
[2] Meerwein and Schmidt, *Ann.*, 1925, **444**, 221 ; Ponndorf, *Z. Angew. Chem.*, 1926, **39**, 138.



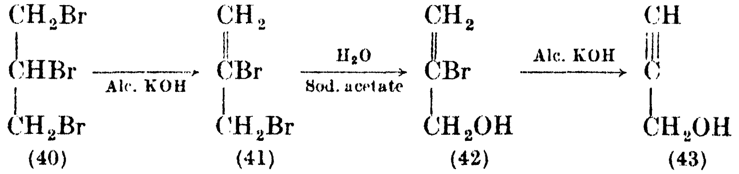
The structure of the final alcohol is, of course, limited to the configuration



$CH{\equiv}C{-}C(a)(b)OH$, but a number of such alcohols are known, and some are used in perfumery. Thus, linalool, a difficult material to obtain from natural sources, is prepared from methylheptenone (37), through the substance 3, 7-dimethyl octyn-1, ene-6, ol-3 (38), which can be reduced to linalool (39)

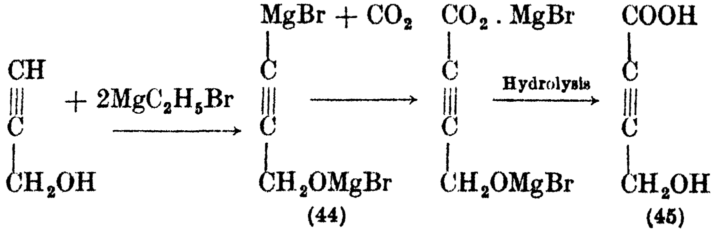


An additional method of producing the acetylenic alcohols, especially propargyl alcohol, is from tribromopropane (glycerol tribromhydrin) (40) or its analogues.



The removal of hydrogen bromide to give 2, 3-dibromopropen-1 (41) is effected by potash, and the hydrolysis to the 2-bromopropen-2, ol-1, is carried out by heating with sodium acetate. This leaves the final removal of hydrogen bromide to be done by alcoholic potash, giving propargyl alcohol (43).

Propargyl alcohol, b. 115°, is miscible with water in all proportions and forms a monohydrate m. – 17°. Oxidation converts it to di-propargyl alcohol,



hexadiyn 2, 4-diol-1, 6. With magnesium ethyl bromide, propargyl alcohol reacts in an unusual manner, giving two molecules of ethane and a di-magnesium derivative (44) which absorbs carbon dioxide rapidly, giving a complex which on decomposition with water, yields γ-oxytetrolic acid (45). Although many other acetylenic alcohols are known, they are not of sufficient importance to warrant description here.

Glycols and Glycerol

In 1783 Scheele[1] published the results of experiments which he had conducted on the 'peculiar saccharine principle in expressed oils and fats', in which he showed that when oils and fats are heated with litharge in the preparation of emplastrum simplex, there is formed a water soluble syrup. He obtained the new substance from a variety of fats, thus showing their common basic principle to be the new sweet compound. He summarised his results thus :—

> " Hence it is seen from this that all fatty oils contain a sweet substance, which differs from sugar and honey in these respects :—
>
> " (1) That it cannot be brought to crystallisation.
>
> " (2) That the sweet substance can not only withstand much stronger heat before it is destroyed, but also that it passes over into the receiver in part unchanged, with retention of its sweetness.
>
> " (3) That it cannot enter into any fermentation.
>
> " (4) That it mixes with spirituous alkaline solutions."

Chevreul, in 1811, named the compound 'glycerol', and he and Berthelot established the trivalent nature of the new alcohol, which appeared to combine with three molecules of a fatty acid to produce fats.

When Wurtz, in 1856, discovered[2] glycol by boiling ethylene di-iodide with silver acetate to give a diacetate which saponified to glycol with alkali, he not only obtained an interesting new substance, but also filled the gap between the monovalent alcohols and the trivalent glycerol ; indeed, it was the presence of this lacuna that induced Wurtz to carry out his experiments on this substance, which he named 'glycol'—" pour marquer la double analogie qui les relie à la glycérine d'une part, à l'alcool de l'autre ".[3]

General methods for the synthesis of glycols are mainly based on the use of halogen derivatives. Thus, when ethylene dichloride is heated with water and a base in an autoclave at 180° the glycol is formed :—

$$\begin{array}{l} CH_2Cl \\ | \\ CH_2Cl \end{array} + 2H_2O \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array} + 2HCl$$

This reaction is the basis of an industrial process for recovery of ethylene from cracker, natural and coke-oven gases ; the ethylene is concentrated by fractionation, allowed to react with chlorine to form the chloride, and the latter heated in autoclaves with ferric hydroxide, producing glycol and ferric chloride solution. In the case of ethylene glycol, the chlorhydrin can be more easily hydrolysed, and this method is used for its industrial production in the U.S.A. The ethylene is allowed to pass with chlorine into sodium hypochlorite solution. The action of chlorine on sodium hypochlorite is to yield hypochlorous acid, which then reacts with the ethylene :—

$$(1)\ NaOCl + Cl_2 + H_2O \longrightarrow 2HOCl + NaCl$$

$$(2)\ 2HOCl + 2C_2H_4 \longrightarrow 2CH_2OH\ .\ CH_2Cl\ \ \begin{array}{c}\text{ethylene}\\ \text{chlorhydrin}\end{array}$$

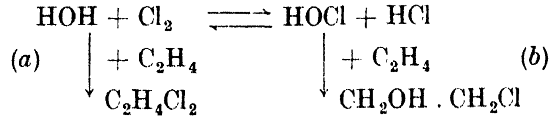
---

[1] Scheele, *Kongl. Vetenskaps. Academiens. Nya Handlingar*, 1783, **4**, 324.

[2] Wurtz, *Ann.*, 1856, **100**, 110.

[3] Wurtz, *Ann. Chem. Phys.*, 1859, (3), **55**, 402.

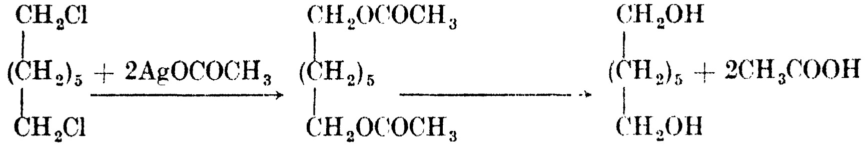
There is produced, at the same time, some ethylene dichloride—Gomberg[1] investigated the reaction closely, and found it could best be represented by the scheme :—



$$\begin{array}{ccccc} & HOH + Cl_2 & \rightleftharpoons & HOCl + HCl & \\ (a) & \downarrow + C_2H_4 & & \downarrow + C_2H_4 & (b) \\ & C_2H_4Cl_2 & & CH_2OH \,.\, CH_2Cl & \end{array}$$

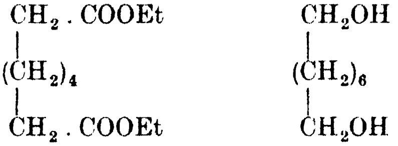
The reaction (*b*) is more rapid than (*a*) and up to about 7 per cent. solutions of ethylene chlorhydrin are obtainable without an appreciable formation of the dichloride. The hydrolysis of the chlorhydrin to the glycol is quite readily brought about by treatment with superheated steam or with mild alkali under pressure.

There are, of course, many other methods by which the halogens of a dichloride can be replaced by hydroxyl ; where the compound is a valuable one and must be conserved, the use of silver acetate followed by hydrolysis is recommended :—



$$\begin{array}{l} CH_2Cl \\ | \\ (CH_2)_5 \\ | \\ CH_2Cl \end{array} + 2AgOCOCH_3 \longrightarrow \begin{array}{l} CH_2OCOCH_3 \\ | \\ (CH_2)_5 \\ | \\ CH_2OCOCH_3 \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ (CH_2)_5 \\ | \\ CH_2OH \end{array} + 2CH_3COOH$$

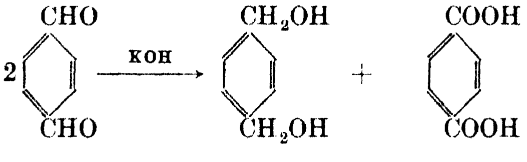
Closely related to this method, is that of Bouveault and Blanc,[2] in which the ester of a dicarboxylic acid is reduced with sodium and alcohol to the glycol :—



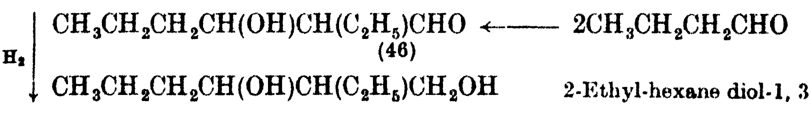
$$\begin{array}{l} CH_2\,.\,COOEt \\ | \\ (CH_2)_4 \\ | \\ CH_2\,.\,COOEt \end{array} \qquad \begin{array}{l} CH_2OH \\ | \\ (CH_2)_6 \\ | \\ CH_2OH \end{array}$$

Octane diol-1, 8

Other substances may be reduced to give glycols, notably the dialdehydes, but owing to the difficulty of obtaining such substances, the method is of little more than theoretical importance, except in the cases of the dialdehydes of the phthalic acid series, which are more easily obtained, and which, on warming with alkali, give a double Cannizzaro reaction. In this way terephthalyl



alcohol can be prepared ; and is, of course, also obtainable from the aldehyde by catalytic reduction. The method of catalytic reduction of aldehydes, particularly unsaturated, or hydoxy, aldehydes is a very fertile method for the



$$\begin{array}{l} CH_3CH_2CH_2CH(OH)CH(C_2H_5)CHO \xleftarrow[(46)]{} 2CH_3CH_2CH_2CHO \\ \Big\downarrow H_2 \\ CH_3CH_2CH_2CH(OH)CH(C_2H_5)CH_2OH \end{array}$$

2-Ethyl-hexane diol-1, 3

synthesis of glycols. Thus, if two molecules of aldehyde are allowed to undergo an aldol condensation, and the product (46) is reduced catalytically a 1-substituted alkylene diol is obtained. This reaction proceeds also with epoxy compounds. Thus, furaldehyde and acetaldehyde condense to give furyl acrolein (47); this on reduction yields the α-ω-diol, in this case, heptane diol-1, 7 (48).

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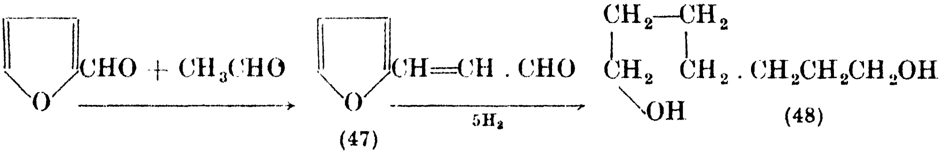
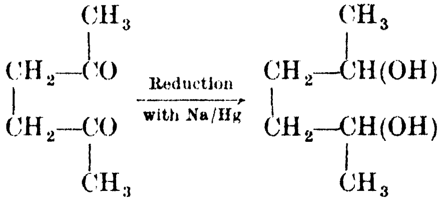
[1] Gomberg, *J.A.C.S.*, 1918, **41**, 1414.

[2] Bouveault and Blanc, *Bull. Soc. Chim.*, 1904, (3), **31**, 1203.



(47) (48)

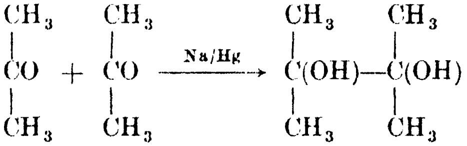
It is only a step from this synthesis to the reduction of diketones, which is capable of yielding disecondary glycols. Thus acetonyl acetone (49), reduced



$$\begin{array}{c} CH_3 \\ | \\ CH_2-CO \\ | \\ CH_2-CO \\ | \\ CH_3 \end{array} \xrightarrow[\text{with Na/Hg}]{\text{Reduction}} \begin{array}{c} CH_3 \\ | \\ CH_2-CH(OH) \\ | \\ CH_2-CH(OH) \\ | \\ CH_3 \end{array}$$

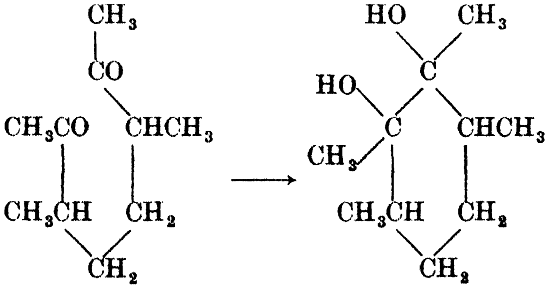
(49) (50)

by sodium amalgam, yields hexanediol-2, 5 (dimethylbutyleneglycol) (50). The reduction of simple ketones yields di-tertiary glycols—as for example, in the well-known reaction when acetone is reduced to pinacol :—



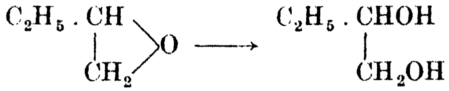
$$\begin{array}{c} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{array} + \begin{array}{c} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{array} \xrightarrow{\text{Na/Hg}} \begin{array}{ccc} CH_3 & & CH_3 \\ | & & | \\ C(OH) & - & C(OH) \\ | & & | \\ CH_3 & & CH_3 \end{array}$$

The reaction just cited is an idealisation of what really occurs; much of the acetone is reduced to *iso*-propyl alcohol, and even a little propane is formed. To increase the yield of pinacol, a mercury-magnesium couple is used. The acetone is used as a solvent for mercuric chloride, which is dropped on to magnesium covered with benzene. A very vigorous reaction ensues, and magnesium pinacol separates as a bulky solid which is fairly easily decomposed to pinacol itself. A long series of pinacols has been prepared by this method, and are convenient starting points in synthetic work. The pinacols are discussed from a theoretical aspect in Chapter IX, Vol. III. If attempts are made to obtain a glycol by the reduction of a diketone in which four or five methylene—or substituted methylene groups—separate the two carbonyl groups, ring formation and an intramolecular pinacol results. An instance is :



3, 6-Dimethyloctane-dione-2, 7 **1, 2, 3, 4-Tetramethyl *cyclo* hexane diol-2, 3**

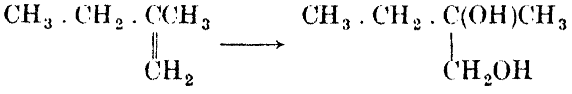
Glycols are also fairly readily obtainable by opening the ring of 1, 2-epoxy compounds with the subsequent addition of the elements of water. The method is almost entirely confined to the preparation of 1, 2-glycols, but the reaction is general and enables a number of the unsymmetrically constructed derivatives of ethylene glycol to be obtained, e.g. ethyl ethylene glycol (52) from ethyl ethylene oxide (51) :—



(51) (52)

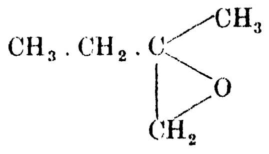
The reaction is brought about by heating the oxide under pressure with water, when the ring opens and the glycol is produced. In favourable instances the reaction can be carried out with dilute acid at 100°.

Glycol Formation by Addition to a Double Bond.—Almost all reference books on organic chemistry refer to the addition of the elements of hydrogen peroxide to the ethylenic double bond with the formation of ethylene glycol; that this is, indeed, a true addition reaction which does not proceed *via* the intermediate formation of an epoxide was shown by Wagner,[1] who oxidised 2-methyl butene-1 (53) with permanganate and obtained the glycol (54), although under exactly identical conditions 1-methyl-1-ethyl ethylene oxide (55) was unaffected. The



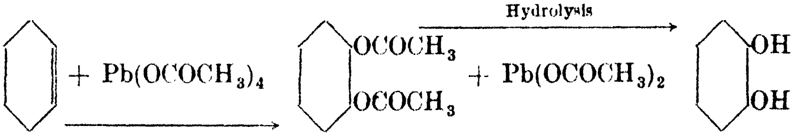
$$CH_3.CH_2.\underset{\underset{CH_2}{\|}}{C}CH_3 \longrightarrow CH_3.CH_2.\underset{\underset{CH_2OH}{|}}{C}(OH)CH_3$$

(53) (54)



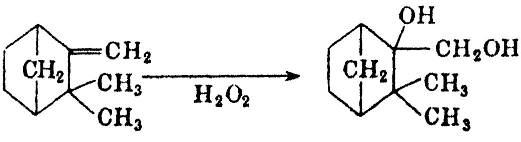
(55)

use of 4-5 per cent. cold aqueous permanganate is recommended for this reaction, but barium permanganate is to be preferred, especially in the presence of magnesium sulphate. The yields, however, are always disappointing, as much of the material is further oxidised. Various other methods have been discovered for the addition of the elements of hydrogen peroxide to a double bond ; one of the most successful is the use of lead tetra-acetate, which forms the diacetyl glycol, in good yield, thus leading to the glycol. An example of its use is Criegee's preparation[2] of *cyclo*hexane diol (58) from *cyclo*hexene (56)



(56) (57) (58)

via the diacetate (57). Again, it is not surprising to find that the action of hydrogen peroxide itself (preferably in acetic acid solution) yields glycols. The reaction appears to be particularly serviceable in the conversion of camphene (59) to camphene diol (60).



(59) (60)

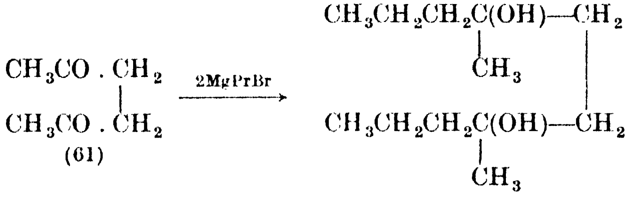
Nothing, so far, has been said concerning the use of Grignard reagents for the production of glycols ; it is obvious that any diketone, keto-aldehyde, dialdehyde, hydroxy aldehyde or ketone, or any substance containing a combination of ester groups with hydroxyl, aldehyde or ketone groups, will, by a suitable application of the Grignard reaction, yield a glycol which usually contains at least one tertiary group. One or two instances are given below :—

---

[1] Wagner, *Ber.*, 1888, **21**, 1230.

[2] Criegee, *Ann.*, 1930, **481**, 263.

(*a*) Acetonyl acetone (61) and magnesium-*n*-propyl bromide give

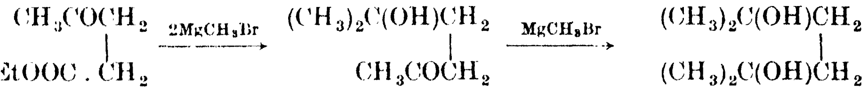


$$\begin{array}{c} CH_3CO\,.\,CH_2 \\ | \\ CH_3CO\,.\,CH_2 \end{array} \xrightarrow{2MgPrBr} \begin{array}{c} CH_3CH_2CH_2C(OH)(CH_3)\text{—}CH_2 \\ | \\ CH_3CH_2CH_2C(OH)(CH_3)\text{—}CH_2 \end{array}$$

(61) (62)

4, 7-dimethyldecane diol-4, 7 (62).

(*b*) Levulic ester (63) gives 2, 5-dimethyl hexane diol-2, 5 (65) through

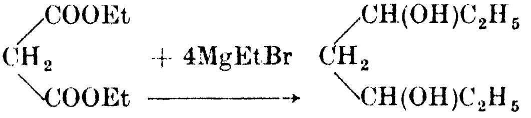


$$\begin{array}{c} CH_3COCH_2 \\ | \\ EtOOC\,.\,CH_2 \end{array} \xrightarrow{2MgCH_3Br} \begin{array}{c} (CH_3)_2C(OH)CH_2 \\ | \\ CH_3COCH_2 \end{array} \xrightarrow{MgCH_3Br} \begin{array}{c} (CH_3)_2C(OH)CH_2 \\ | \\ (CH_3)_2C(OH)CH_2 \end{array}$$

(63) (64) (65)

the intermediate formation of the keto- alcohol (64). The result of this reaction is, therefore, exactly the same as if acetonyl acetone had been used as the starting material ; as, in many cases, the keto- esters are more readily obtainable, they are preferred. The process reaches its logical conclusion in the interaction of the esters of dibasic acids to give the glycols, as in example :—

(*c*) where malonic ester, in the presence of an excess of magnesium ethyl bromide, gives heptane diol-3, 5 (66).



$$CH_2(COOEt)_2 + 4MgEtBr \longrightarrow CH_2(CH(OH)C_2H_5)_2$$

(66)

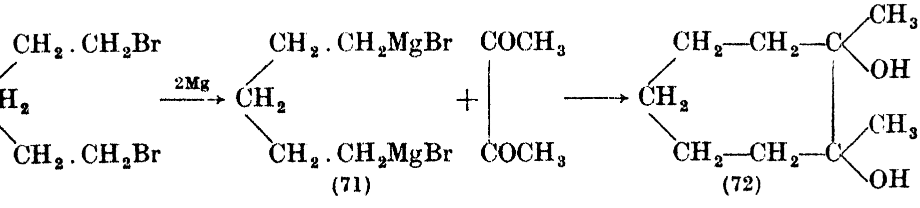
(*d*) The Grignard reagent from an alkylene dibromide is capable of reacting with formaldehyde to give a glycol, or with an α-diketone to give a cyclic glycol. Thus, 1, 7-dibromoheptane, converted to its double Grignard compound (67) and the latter allowed to react with formaldehyde gives nonane diol-1, 9 (70),

$$BrCH_2(CH_2)_5CH_2Br \xrightarrow{+\,Mg} \underset{(67)}{BrMgCH_2(CH_2)_5CH_2MgBr}$$

$$\xrightarrow[+2CH_2O]{} \underset{(70)}{HOCH_2CH_2(CH_2)_5CH_2CH_2OH}$$

which is identical with that obtained by the method of Bouveault and Blanc from the diethyl ester of azelaic acid.

By using an α-diketone, cyclic compounds may be obtained as in Grignard and Vignon's synthesis[1] of 1, 2-dimethyl *cyclo*heptane diol-1, 2 (72) from



$$CH_2(CH_2.CH_2Br)_2 \xrightarrow{2Mg} CH_2(CH_2.CH_2MgBr)_2 + \begin{array}{c} COCH_3 \\ | \\ COCH_3 \end{array} \longrightarrow \begin{array}{c} CH_2\text{—}CH_2\text{—}C(CH_3)(OH) \\ CH_2 \qquad\qquad | \\ CH_2\text{—}CH_2\text{—}C(CH_3)(OH) \end{array}$$

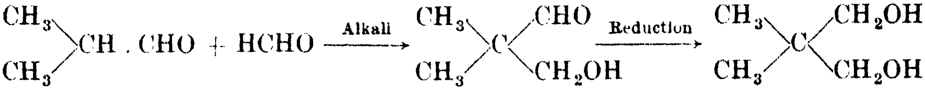
(71) (72)

dibromopentane, through its magnesium derivative (71).

---

[1] Grignard and Vignon, *C.R.*, 1907, **144**, 1358.

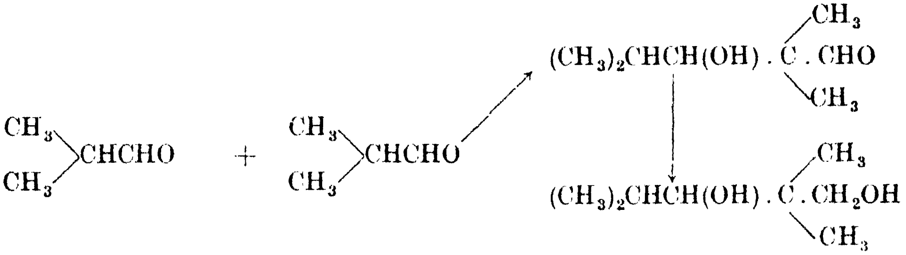
It may be added here that the aldol condensation followed by reduction is a prolific source of glycols; thus *iso*-butyraldehyde and formaldehyde react to



(73) (74)

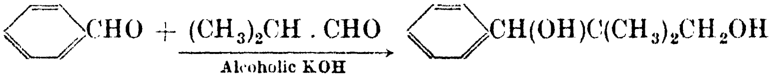
give the hydroxy aldehyde (73); this, on reduction, gives 2, 2-dimethylpropane diol-1, 3 (74). This constitutes a valuable method of obtaining the primary glycols.

The condensation of two molecules of *iso*-butyraldehyde leads to a complex



2, 2, 4-Trimethylpentane diol-1, 3 (75)

glycol, 2, 2, 4-trimethyl pentane diol-1, 3 (75) by reduction of the intermediate aldol. The use of dilute alcoholic potash for the preparation of aldols of the semi-aromatic type, often leads to the formation of glycols direct, part of the ethanol being oxidised. This gives, in the case of benzaldehyde and *iso*-butyraldehyde (76), 2, 2-dimethyl-1-phenyl propane-diol-1, 3 (77).



(76) (77)

In addition to the reactions already described for the preparation of glycols there are a number of methods which are of constitutional significance only. Examples of such are

(*a*) the treatment of aliphatic diamines with nitrous acid to give the corresponding glycol :—

$$NH_2(CH_2)_nNH_2 \xrightarrow{2HNO_2} HO(CH_2)_nOH + 2H_2O + 2N_2$$

(*b*) the reduction of unsaturated glycols to saturated compounds;

(*c*) the hydrolysis of glycol esters;

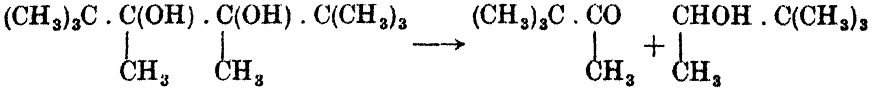
(*d*) the reduction of polyhydroxy compounds with formic acid, e.g. erythrite, or mannite;

(*e*) the intramolecular condensation of alcohols under the influence of ultraviolet light :—

$$2C_2H_5OH \longrightarrow CH_3CH(OH)CH(OH)CH_3$$

GENERAL PROPERTIES OF THE GLYCOLS

(1) Whilst the majority of glycols are less stable than the normal monohydric alcohols, they exhibit greater stability than the dialdehydes and diketones. In certain instances, especially if two of the carbon atoms adjacent to the glycol structure are tertiary, the glycols exhibit a tendency to dissociate :—

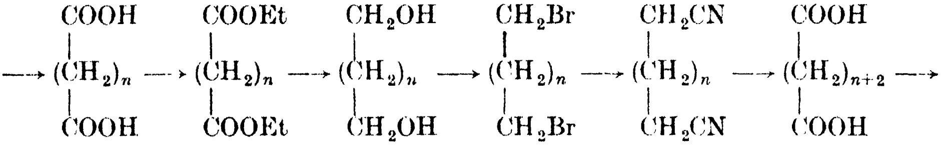


$$(CH_3)_3C\cdot\underset{CH_3}{C}(OH)\cdot\underset{CH_3}{C}(OH)\cdot C(CH_3)_3 \longrightarrow (CH_3)_3C\cdot\underset{CH_3}{C}O + \underset{CH_3}{C}HOH\cdot C(CH_3)_3$$

(78) (79) (80)

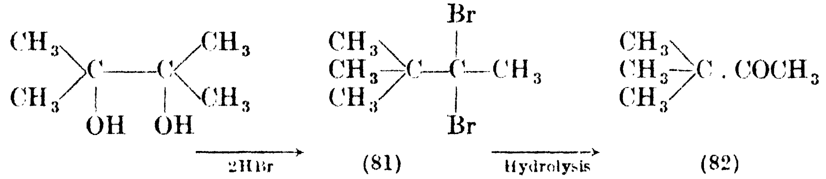
Thus, symmetrical dimethyl di-*tertiary* butyl ethylene glycol (78) decomposes into *ter*-butyl methyl ketone (79) and *ter*-butyl methyl carbinol (80); the latter soon dehydrates and rearranges to tetramethyl ethylene.

(2) The action of halogen acids on glycols is precisely what might have been expected from analogy with the monohydric alcohols, namely, the formation of the corresponding halides. The reaction constitutes an important step in the synthesis of higher dibasic acids from the lower members of the series, as shown in the sequence of formulæ below :—



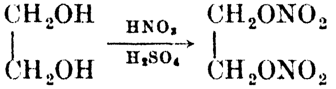
$$\begin{matrix}COOH\\|\\(CH_2)_n\\|\\COOH\end{matrix}\longrightarrow\begin{matrix}COOEt\\|\\(CH_2)_n\\|\\COOEt\end{matrix}\longrightarrow\begin{matrix}CH_2OH\\|\\(CH_2)_n\\|\\CH_2OH\end{matrix}\longrightarrow\begin{matrix}CH_2Br\\|\\(CH_2)_n\\|\\CH_2Br\end{matrix}\longrightarrow\begin{matrix}CH_2CN\\|\\(CH_2)_n\\|\\CH_2CN\end{matrix}\longrightarrow\begin{matrix}COOH\\|\\(CH_2)_{n+2}\\|\\COOH\end{matrix}\longrightarrow$$

The tendency shown towards a pinacol/pinacone change is exhibited by the halides of ditertiary glycols, and if pinacol is subjected to the action of concentrated hydrobromic acid, a dibromo compound is obtained (81) corresponding in carbon structure to that of pinacone, into which it is converted by hydrolysis (82) :—



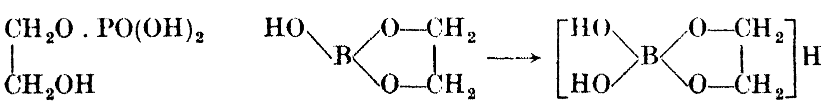
(81) (82)

(3) Glycols react readily with nitric acid to form the dinitrate



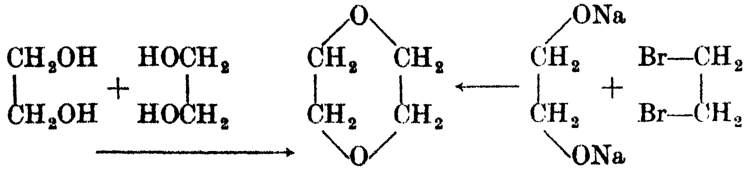
$$\begin{matrix}CH_2OH\\|\\CH_2OH\end{matrix}\xrightarrow[H_2SO_4]{HNO_3}\begin{matrix}CH_2ONO_2\\|\\CH_2ONO_2\end{matrix}$$

One of the characteristics of the polyhydric alcohols is the ease with which these nitric esters are formed. The compound delineated above is often called ' nitroglycol ', but the more systematic term glycol dinitrate is to be preferred. Phosphoric acid forms the mono ester (83), but boric acid has a special mode



(83) (84) (85)

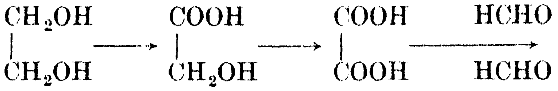
of esterification which characterises all substances containing a 1, 2-glycol structure. An additional hydroxyl group becomes associated with the boron, and an acid is created by the expulsion of a proton. In this way a moderately strong acid is produced, much stronger than boric acid itself. This formation explains the analytical procedure of adding glycol, glycerol or mannitol to boric acid solutions to obtain a solution suitable for titration. The esterification and etherification of glycols proceeds normally, di-esters being obtained. Many of



(86) (87)

the esters, half esters, ethers and ether-esters of ethylene glycol are valuable solvents, and are manufactured in industrial quantities. Ethylene glycol forms an internal double ether (86) 'dioxane', which is not only a valuable solvent but, when sufficiently purified, is also an excellent cryoscopic medium for molecular weight determinations. Dioxane can also be obtained by treating di-sodio ethylene glycol with ethylene dibromide (87).

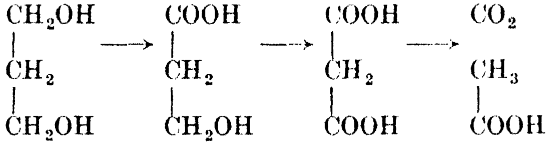
Glycols are readily oxidised, but it is more convenient to discuss the products formed in connexion with each individual glycol. In general it may be said that the main stages in the oxidation of ethylene glycol are glycollic acid, oxalic acid, and formaldehyde :—



$$\begin{array}{l}CH_2OH\\ |\\ CH_2OH\end{array} \longrightarrow \begin{array}{l}COOH\\ |\\ CH_2OH\end{array} \longrightarrow \begin{array}{l}COOH\\ |\\ COOH\end{array} \longrightarrow \begin{array}{l}HCHO\\ \\ HCHO\end{array}$$

This reaction takes place biochemically as well as *in vitro*, and it is this fact which precludes the use of ethylene glycol as a solvent for medicinal and flavouring agents ; in addition, the ethers of ethylene glycol have an intrinsic toxicity which makes them dangerous, especially in the case of dioxane.

On the other hand, 1, 3-propylene glycol (88) forms malonic and acetic acids as stages in its biological or chemical oxidative degradation :—

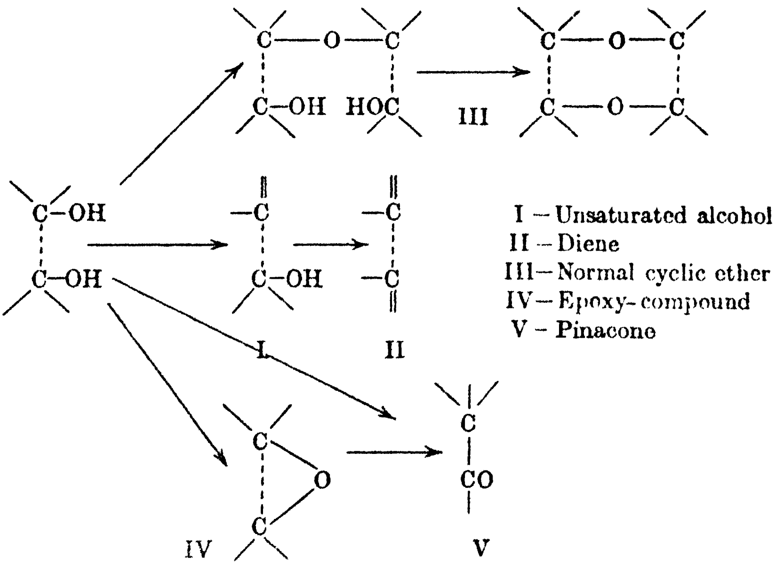


$$\begin{array}{l}CH_2OH\\ |\\ CH_2\\ |\\ CH_2OH\end{array} \longrightarrow \begin{array}{l}COOH\\ |\\ CH_2\\ |\\ CH_2OH\end{array} \longrightarrow \begin{array}{l}COOH\\ |\\ CH_2\\ |\\ COOH\end{array} \longrightarrow \begin{array}{l}CO_2\\ \\ CH_3\\ |\\ COOH\end{array}$$

(88)

This makes propylene glycol much more suitable for medicinal or food usage.

The dehydration of glycols can take place in a variety of ways ; the products obtained being dependent largely on the structure of the glycol, although the conditions of reaction also affect its course. The five principal methods of dehydration are indicated in the scheme below :—



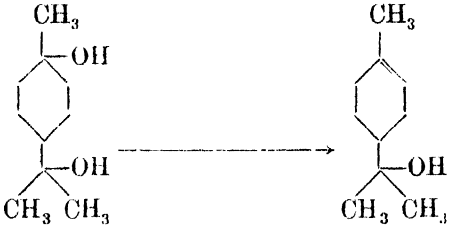
I – Unsaturated alcohol
II – Diene
III – Normal cyclic ether
IV – Epoxy-compound
V – Pinacone

The reactions proceed simultaneously, and it is always difficult to get one to proceed with entire exclusion of the others. The formation of unsaturated alcohols is observed only with a few uncommon α or β glycols, or cyclane diols.

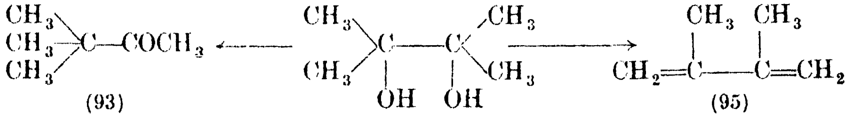
A typical instance is the action of traces of iodine on 2, 4-dimethylpentane

$$\underset{(89)}{(CH_3)_2C(OH)CH_2C(OH)(CH_3)_2} \longrightarrow \underset{(90)}{(CH_3)_2C{=}CH\,.\,C(OH)(CH_3)_2}$$

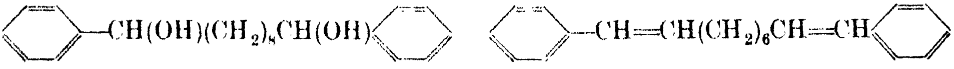
diol 2, 4 (89), which leads to 2, 4-dimethyl pentene-2, ol-4 (90). In the cyclane series the partial dehydration of 1, 8-terpin (91) to terpineol (92) is an excellent example of this reaction :—


(91) (92)

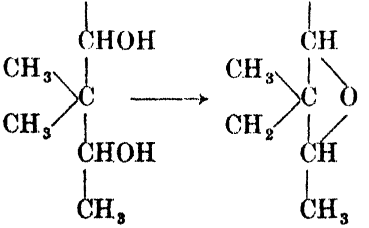
The formation of dienes by the dehydration of glycols is a reaction which accompanies the pinacone transformation, and in some cases almost obscures it. Thus, pinacol (94) heated with small quantities of sulphuric acid yields the diene (95) in large yield ; with dilute sulphuric acid in the warm, or by standing in the cold with more concentrated acid, the pinacone (93) is the preponderating product :—

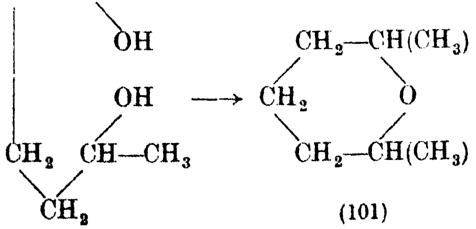

(93) (94) (95)

when, however, the hydroxyl groups are so far apart as to be almost independent, the reaction proceeds almost exclusively to the diene—such an instance is diphenyl decane diol[1] (96) which on dehydration with zinc chloride gives an excellent yield of diphenyl decadiene (97) :—


(96) (97)

The formation of epoxides from α-glycols is not easy and the yields are very poor ; thus, ethylene glycol gives a very low yield of ethylene oxide by dehydration—most of the product being a mixture of the mono ether and dioxane. In the case, however, of β-glycols doubly substituted in the central carbon atom, oxide formation proceeds satisfactorily, e.g.


(98) (99)


(100) (101)

3, 3-dimethylpentane diol-2, 4 (98) yields the 1, 2, 2, 3-tetramethyl " propylene oxide " (99) (better called 3, 3-dimethyl 2, 4-epoxypentane), whilst in the case of 1, 4- and 1, 5-glycols the formation of the epoxy compound is the normal course of the reaction, e.g. heptane diol 2, 6 (100) gives 2, 6-epoxyheptane (101).

---

[1] Losanitch, *C.R.*, 1911, **153**, 390.

Several references have been made to the pinacol-pinacone transformations, and it is necessary at this stage to point out that the change referred to by this name is merely one of a long series of similar rearrangements, many of which have importance as synthetic processes. Thus primary-secondary or primary-tertiary α-glycols yield aldehydes, e.g. in (*a*) and (*b*) below, whilst

$$(a)\ (CH_3)_2C(OH)\text{—}CH_2OH \xrightarrow[-H_2O]{} (CH_3)_2CH\,.\,CHO$$

$$(b)\ CH_3\,.\,CH(OH)CH_2OH \xrightarrow[-H_2O]{} CH_3CH_2CHO$$

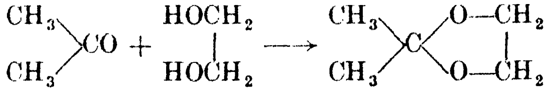
$$(c)\ C_6H_5\,.\,CH(OH)CH(OH)CH_3 \xrightarrow{-H_2O} C_6H_5CH_2\,.\,COCH_3$$

in (*c*) the conversion of a di-secondary glycol to a ketone is indicated. Again, in the case of secondary-tertiary glycols numerous transpositions can occur, the nature of which are outside the scope of this book.

Some Individual Glycols

Enough has been said during the previous survey of synthetic methods for the preparation of glycols, to cover all the important processes by which glycol is obtained. The industrial synthesis from hypochlorous acid and ethylene followed by hydrolysis of the chlorhydrin so produced, is used on a very considerable scale.

Ethylene glycol is a syrupy liquid, considerably more viscous than ethanol, and less viscous than glycerol; it has a sweet taste, and is miscible with water and alcohol in all proportions. It has m.p. − 12·3°,[1] and boils at 197·5°. It is used for a variety of industrial purposes—particularly as an anti-freeze material, and for the preparation of its esters for use as solvents. It readily forms a cyclic acetal with acetone (102), which is quite stable and boils at



(102)

92·6°; this behaviour is characteristic of α-glycols, and is of great value in the study of the sugars, where the cyclic acetals of the hexoses afford more easily crystallised products than are the sugars themselves, whilst the 'blocking' of the groups by acetone affords a means of localising the action of other reagents.

The conversion of glycol to its esters and ethers follows a normal course and, in view of the particularly important part played by these esters in the solvent and lacquer industry, it is proposed to summarise their properties in Table III instead of disseminating the data through the special sections appropriate to esters and ethers.

The mono ethers are known as the 'cellosolve' family; 'cellosolve' itself is the ethyl derivative; the others are called "methyl", "propyl", and "butyl cellosolve".

Dioxane is obtained[2] by direct dehydration of the glycol by heating with 4 per cent. of its weight of sulphuric acid, or by heating it with ferric sulphate.[3]

---

[1] Parks and Kelley, *J.A.C.S.*, 1925, **47**, 2089.

[2] Favorski, *J. Russ. phys.-chem. Soc.*, 1906, **38**, 741.

[3] van Alphen, *Rec. Trav. Chem.*, 1930, **49**, 104.

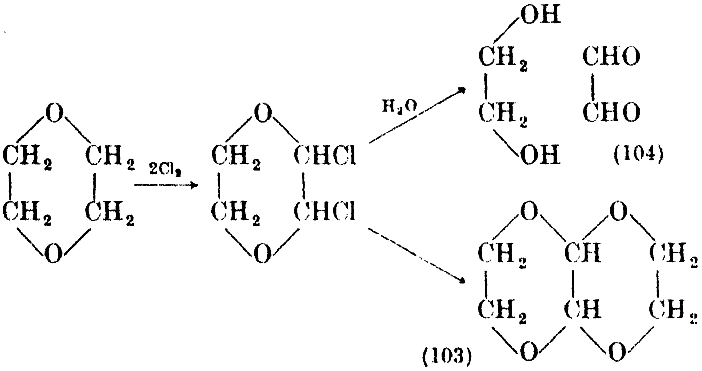
Dioxane can be isolated by steam distillation, but dioxane and water form a mixture, boiling at 90° from which the former must be thrown out by saturation with salt (NaCl).

TABLE III

SOME ETHYLENE GLYCOL ESTERS AND ETHERS

Derivative	Mono-compound		Di-compound	
	B.P.	Density	B.P.	Density
Esters				
Formic . .	179-180°	0·199/50°	174°	1·193/0°
Acetic . . .	187-189°		190°	1·109/15°
Butyric . .	220°		240°	1·024/0°
Stearic . .			— m. 52-5°	
Benzoic . .	176-180°/720 mm. (m. 45°)		360° m. 73-4°	
Ethers				
Methyl . .	125-126°	0·9647/20°	82-83°	0·8628/20°
Ethyl . . .	135-136°	0·9297/20°	123°	0·8484/20°
n-Propyl . .	150-151°	0·9135/20°	160-161°	0·8389/20°
n-Butyl . .	171-172°	0·901°	195-196°	
Amyl . .	182°	0·8926°		
Phenyl . .	147°/25 mm.		154°/2 mm.	
Benzyl . .	134-135°/13 mm.			

Dioxane is a liquid (m. 11°, b. 102°) which has unusual properties; it appears in many ways to behave as an oxonium compound, forming stable 'salts' with sulphuric acid, and with metallic halides. It can be chlorinated to give a 2, 3-dichloro derivative, which reacts with ethylene glycol to give naphthodioxane (m. α, 109-112°; m. β, 133-136° (103). 2, 3-Dichlorodioxane may be hydrolysed to glyoxal (104).



Naphthodioxane
α form m. 109-112°
β form m. 133-136°

The properties of some of the homologous glycols are shown in Table IV.

Of the glycols mentioned in Table IV, propylene glycol-1, 2 has a special interest as being available in industrial quantities, from the propylene isolated from cracker gas; butane diol-2, 3 is also of considerable biochemical interest, since it is obtained in many fermentations as an intermediate between the sugars and the final products. In some cases it is possible to arrest the further decomposition of the glycol and to isolate the glycol in a pure state; this is so in the case of the fermentation of glucose by *B. Asiaticus mobilis*, when about one quarter of the weight of glucose used can be recovered as butane diol-2, 3.

TABLE IV

SOME GLYCOLS

Name	Formula	M.P.	B.P.		Other data
Propane diol-1, 3	$HOCH_2 . CH_2CH_2OH$	—	216°		d^{20} 1·0597
Butane diol-1, 4	$HOCH_2(CH_2)_2CH_2OH$	19°	235°		d^{20} 1·020
Pentane diol-1, 5	$HOCH_2(CH_2)_3CH_2OH$	—	236°		d^{18} 0·994
Hexane diol-1, 6	$HOCH_2(CH_2)_4CH_2OH$	42°	250°		Diphenyl urethane m. 172°
Heptane diol-1, 7	$HOCH_2(CH_2)_5CH_2OH$	22·5°	262°		„ m. 137°
				mm.	
Octane diol-1, 8	$HOCH_2(CH_2)_6CH_2OH$	62·3°	164°	12	„ m. 172°
Nonane diol-1, 9	$HOCH_2(CH_2)_7CH_2OH$	46°	177°	15	
Decane diol-1, 10	$HOCH_2(CH_2)_8CH_2OH$	74·5°	179°	15	
Undecane diol 1, 11	$HOCH_2(CH_2)_9CH_2OH$	62·5°	178°	12	Diacetate b. 181-3′/13 mm.
Dodecane diol-1, 12	$HOCH_2(CH_2)_{10}CH_2OH$	81°	185°	8	„ m. 36°
Tridecane diol-1, 13	$HOCH_2(CH_2)_{11}CH_2OH$	76·4°	196°	10	—
Tetradecane diol-1, 14	$HOCH_2(CH_2)_{12}CH_2OH$	85°	200°	9	—
Pentadecane diol-1, 15	$HOCH_2(CH_2)_{13}CH_2OH$	88°	—	—	Diacetate m. 36°
Hexadecane diol-1, 16	$HOCH_2(CH_2)_{14}CH_2OH$	91·5°	197·9°	3	„ m. 47·2°
Heptadecane diol-1, 17	$HOCH_2(CH_2)_{15}CH_2OH$	96·5°	204·5°	2	
Octadecane diol-1, 18	$HOCH_2(CH_2)_{16}CH_2OH$	98·6°	210-11°	2	
Nonadecane diol-1, 19	$HOCH_2(CH_2)_{17}CH_2OH$	101°	212·4°	1·5	
Eicosane diol-1, 20	$HOCH_2(CH_2)_{18}CH_2OH$	103°	215·7°	1·5	
Heneicosane diol-1, 21	$HOCH_2(CH_2)_{19}CH_2OH$	105°	223·4°	1·5	„ m. 60°
Propane diol-1, 2	$HOCH_2 . CH(OH)CH_3$	—	188·9°		d 1·051
Butane diol-2, 3	$CH_3CH(OH)CH(OH)CH_3$	41°	racemic		Diphenyl urethane m. 201°-202°
		34·4	meso		Diphenyl urethane m. 175°
Butane diol-1, 2	$CH_3.CH_2CH(OH)CH_2OH$	—	91·2°/15 mm.		Gives *d*- and *l*-forms
Dimethyl-2, 3 butane diol-2, 3	$(CH_3)_2C(OH).C(OH)(CH_3)_2$	36°	171·2°		Pinacol (or pinacoline)

Unsaturated glycols are known, those belonging to the acetylene series being particularly easy to obtain from the dimagnesium derivative of dibromo acetylene. For example, with formaldehyde (trioxymethylene serves) it gives

$$2CH_2O + BrMgC{\equiv}CMgBr \longrightarrow HOCH_2 . C{\equiv}C . CH_2OH$$

(105)

butyne-2, diol-1, 4 (105) a stable substance which is capable of distillation (b. 157°) without appreciable decomposition. The reaction is general, and higher members of the series can be obtained by the use of the appropriate aldehyde, e.g. :—

$$2CH_3CHO + BrMg . C{\equiv}C . MgBr \longrightarrow CH_3CH(OH) . C{\equiv}C . CH(OH)CH_3$$

Hexyne-3, diol-2, 5

GLYCEROL AND THE TRIOLS

Although, apart from glycerol, triols are infrequently encountered, many have been prepared, one or two of which are described later; it is proposed, however, to discuss the chemistry of glycerol first. Many syntheses of glycerol have been described, one of which is the elegant method of Pictet and Barbier,[1] in which glycollic aldehyde is allowed to react with nitromethane (106) in the presence of potassium bicarbonate to give a true nitroglycol (107), which is reduced to the amine (108) by amalgamated aluminium and converted to glycerol by nitrous acid in absolute alcohol (109).

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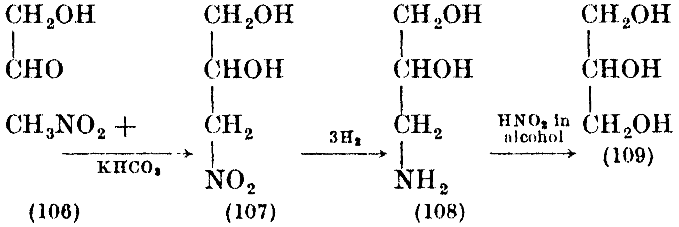
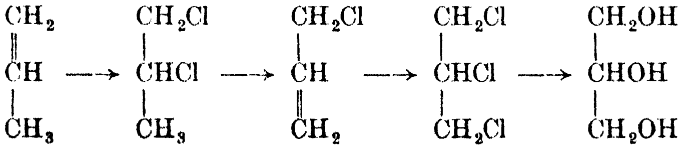
[1] Pictet and Barbier, *H. Ch. Acta*, 1921, **4**, 924.



Other syntheses involve the hydrolysis of 1, 2, 3-trichloropropane and the reduction of dihydroxyacetone, whilst a variety of syntheses, now relatively unimportant, centre round the formation of glyceric aldehyde from acrolein, and dihydroxy acetone from formol and nitromethane, the latter reaction being discovered by Piloty.[1]

So far, little success has attended the preparation of glycerol by purely synthetic means, although a plant has been erected for this process in the U.S.A. The matter is largely one of economics ; since glycerol is produced as a by-product in the soap industry its basic cost, provided the demand remains within the scope of available supplies, is purely a matter of the extraction cost. If, therefore, a synthetic process for glycerol production is to compete with the recovery process, its costs, including that of raw and ancillary materials, must be less than the cost of recovery from the sweet liquors[2] of the soap industry. It is clear that the only three-carbon compound available on an industrial scale, which could serve as a source of glycerol, is propylene ; this would have to pass through the following stages :—



The steps in this synthesis are all readily accomplished by simple reagents, and are reasonably quantitative in performance, but the conversion of 142 kg. of chlorine to hydrochloric acid for each 36 kg. of propylene treated (or for each 85 kg. of glycerol produced) is, in itself, a very considerable economic ' millstone ' for the process to carry.

Industrially, the liquors from the saponification of the triglycerides of fats are the main raw materials for the production of glycerol ; there is, in addition, an increasingly large amount of liquor from the aqueous hydrolysis of fats under pressure in the presence of catalysts. The neutral liquor is vacuum evaporated and the glycerin removed from the concentrate by distillation with superheated steam *in vacuo*.

A third method is available for the production of glycerol, namely, the fermentation of glucose, or of molasses by special yeasts, in the presence of sulphites. This is an application of the well-known fact that glycerol is produced to the extent of some 3 per cent. in nearly all fermentations ; the yield can be increased to 20-25 per cent. by diverting the course of the fermentation with sulphites.

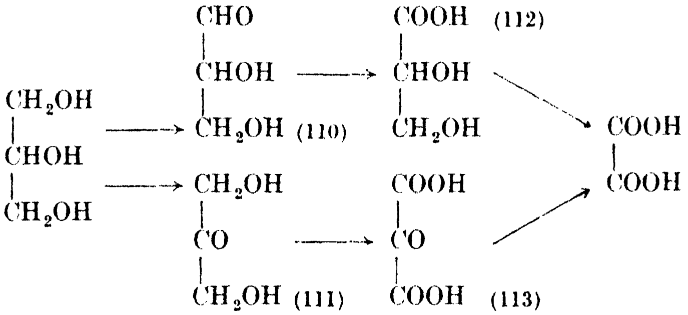
---

[1] Piloty, *Ber.*, 1897, **30**, 3161.

[2] ' Sweet liquor ' is the fluid remaining after the soap has separated from the solution obtained by the saponification of a fat.

Glycerol is normally seen as a liquid of very high viscosity; its m.p. is 18-19°, so that for a considerable portion of the year it will exist in the supercooled condition. The crystallisation of glycerol is induced by nuclei of the solid material, and once started in a large scale plant can be a profound nuisance; such solidification renders the emptying of drums only possible after prolonged thawing and blocks pipes, etc.; it is fortunately of rare occurrence. When pure, glycerol distils unchanged at 290°—in the presence of water or metallic salts it decomposes on distillation with the formation of some acrolein.

The chemical properties of glycerol are largely those of an aliphatic alcohol; oxidation produces glyceric aldehyde (110) or dihydroxy acetone (111), or a mixture of both, often called 'glycerose'; further oxidation gives rise to glyceric acid, tartronic acids (112 and 113), whilst even stronger measures lead to oxalic acid:—



Reduction of glycerol gives successively propylene glycol, *n*-propyl alcohol and propane, whilst dehydration gives, if persisted in at temperatures of 285-295°, a polyglycerol. On the other hand, when glycerol is dehydrated more vigorously, e.g. by passing through a tube heated to 450°, a fracture of the chain occurs, in which acetaldehyde and formaldehyde are the main products:—

$$\begin{array}{l} \mathrm{CH_2OH\,.\,CHOH\,.\,CH_2OH} \longrightarrow \\ \qquad\qquad [\mathrm{CH_2OH\,.\,C(OH){=}CH_2}] \longrightarrow \mathrm{CH_2OHCOCH_3} \longrightarrow \\ \qquad\qquad\quad \downarrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad \mathrm{CH_3CHO + HCHO} \\ [\mathrm{CH_2OH\,.\,CH{=}CH(OH)}] \longrightarrow \mathrm{CH_2OH\,.\,CH_2\,.\,CHO} \longrightarrow \mathrm{CH_2{=}CH\,.\,CHO} \end{array}$$

The diagram also shows the decomposition of glycerol to acrolein, probably through the steps shown; in practice acrolein is obtainable in fairly good yield from glycerol by distillation with potassium acid sulphate.

Halogen acids differ considerably in their action on glycerol; hydrochloric and hydrobromic acid convert glycerol to the chlorohydrins and bromohydrins, but hydriodic acid gives allyl iodide and some propylene. Esters and ethers are readily formed from glycerol, and whilst the esters with fatty acids constitute the fats (*q.v.*), the ethers and simpler esters are largely used in the solvent industry. The trinitric ester—known as 'nitroglycerin'—was discovered by Sobrero[1] in 1847, by the usual nitration methods. He noticed its peculiar physiological action but, luckily, did not observe its explosive properties; this remained for Nobel[2] in 1867. Some properties of glyceryl ethers are given in Table V.

The great technical and industrial importance of glycerol somewhat obscures the other triols of which a large number is known. The alkyl glycerol type,

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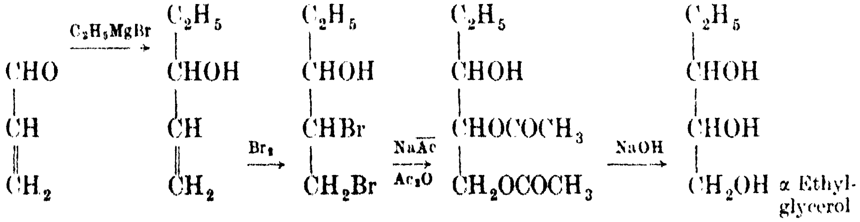
[1] Sobrero, *C.R.*, 1847, **24**, 247.
[2] Nobel, *Dingl. Poly. Journal*, 1867, **183**, 221.

TABLE V

SOME GLYCERYL ETHERS

Substituent groups	α-Mono-ethers			α, γ-Di-ethers			α, β, γ-Tri-ethers		
Ethyl .	b	222°	$d_{4^\circ}^{25^\circ}$ 1·063	b	191°	$d_{4^\circ}^{25^\circ}$ 0·952	b	181°	$d_{4^\circ}^{25^\circ}$ 0·866
Propyl .	b	118-22°/15 mm.	$d_{4^\circ}^{18^\circ}$ 1·074	b	216-18°	$d_{4^\circ}^{25^\circ}$ 0·926	b	232°	
i-Propyl .				b	198-99°	$d_{4^\circ}^{25^\circ}$ 0·914			
Butyl .	b	138-40°/22 mm.	$d_{4^\circ}^{18^\circ}$ 1·002						
ter-Butyl .				m	28°	$d_{4^\circ}^{15^\circ}$ 0·921			
iso-Amyl .	b	254°	$d_{4^\circ}^{25^\circ}$ 0·976	b	265°	$d_{4^\circ}^{25^\circ}$ 0·901			
Hexyl .				b	180°/30 mm.	$d_{4^\circ}^{15^\circ}$ 0·987			
Octyl .				b	234°/30 mm.	$d_{4^\circ}^{15^\circ}$ 0·990			
Hexadecyl	m	64-5°							
Octadecyl .	m	70-71°							
Allyl .	b	240° decomp.	$d_{4^\circ}^{25^\circ}$ 1·1013	b	225-27°	$d_{4^\circ}^{25^\circ}$ 0·991			
Oleyl .	b	236-39°/5 mm.							
Phenyl .	m	67-8°	b. 185-7°/15 mm.	m	80-1°				
o-Chloro-phenyl .	m	65°	b. 250°/19 mm.						
p-Chloro-phenyl .	m	80°	b. 214°/19 mm.						
Benzyl .	b	164-66°/2 mm.	$d_{4^\circ}^{25^\circ}$ 1·130	b	198-204°/2 mm.	$d_{4^\circ}^{25^\circ}$ 1·101			
Tritryl .	m	92-4°		m	174-76°				

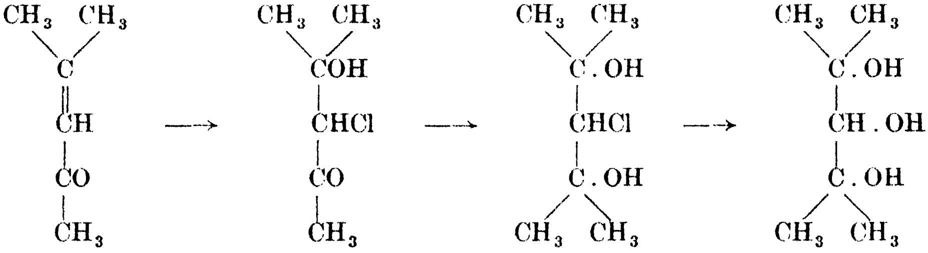
R . CHOH . CHOH . CH_2OH, is prepared by the following sequence of reactions from acrolein :—



The alkyl glycerols resemble glycerol in physical properties, e.g.

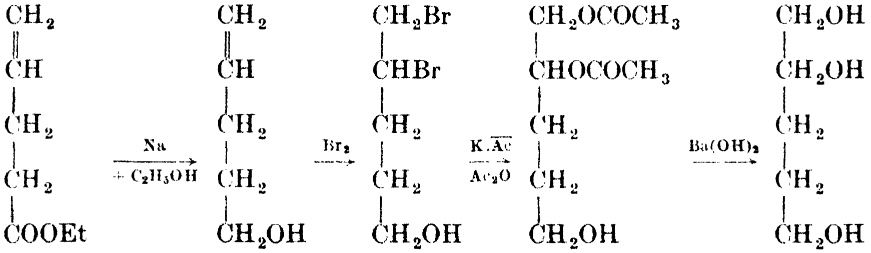
α-Methyl glycerol CH_3 . CHOH . CHOH . CH_2OH b. 162-164°/15 mm.
α-Ethyl glycerol C_2H_5 . CHOH . CHOH . CH_2OH b. 165-166°/15 mm.
α-Propyl glycerol C_3H_7 . CHOH . CHOH . CH_2OH m. 60-62°, b. 167-168°/14 mm.
α-Butyl glycerol C_4H_9 . CHOH . CHOH . CH_2OH m. 53-54°, b. 175-176°/17 mm.

Higher members of this series are related to sphingosine (*q.v.*), which appears to be a pentadecylene glycerol derivative. Many other substituted glycerols have been prepared in which a number of smaller groups have been substituted in the available positions. An example is sym-αα$\alpha'\alpha'$-tetramethyl glycerol (112), which is prepared by the following steps from mesityl oxide (113):—

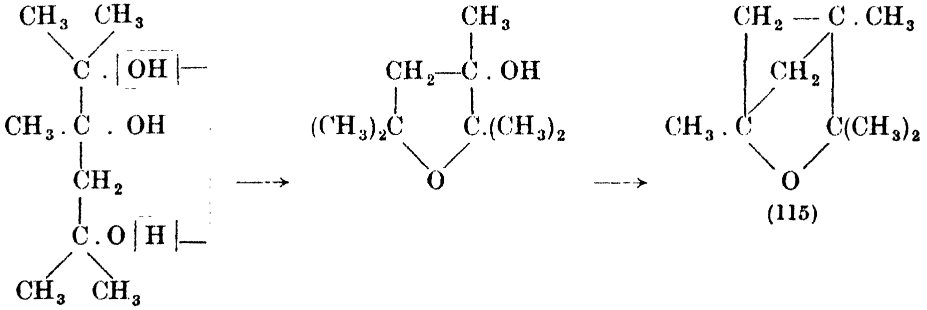


(113) (112)

The triols in which the three hydroxyl groups are not attached to adjacent carbon atoms are fairly numerous; the methods by which they are prepared are, in general, adaptations of the methods which have been previously described; thus, pentanetriol-1, 2, 5 is obtained by the following sequence of operations:—

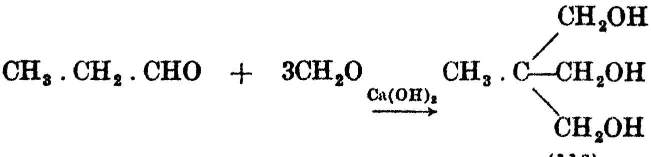


One triol, 2, 3, 5-trimethylhexanetriol-2, 3, 5 (114) is produced in moderate yield with pinacol during the reduction of acetone with sodium amalgam. It is a very viscous syrup, easily soluble in water and is readily transformed by oxalic acid, first into a tetrahydrofurane derivative and then to the bicyclic compound (115).



(114) (115)

Another member of this series, in which the three hydroxyl groups are isolated from each other, is the so-called 'pentaglycerol'. This is 2-methyl-2, methylol propanediol-1, 3 obtained by the condensation of one molecule of propionaldehyde with three molecules of formaldehyde (116):—



$$CH_3.CH_2.CHO + 3CH_2O \xrightarrow{Ca(OH)_2} CH_3.C(CH_2OH)_3$$

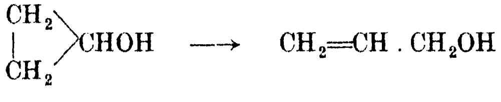
(116)

Unlike glycerol, pentaglycerol is a crystalline solid, m. 199°, which sublimes without decomposition. It is, of course, easily soluble in water; its trinitric ester has explosive properties similar to those of glyceryl trinitrate.

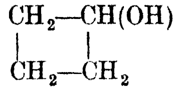
The tetra-, penta- and hexa- hydroxy- compounds are dealt with under the heading of 'carbohydrates' in view of their peculiar relation to the sugars.

THE HYDROXY CYCLANES

Attempts to prepare *cyclo*propanol (117) have proved unavailing, and only

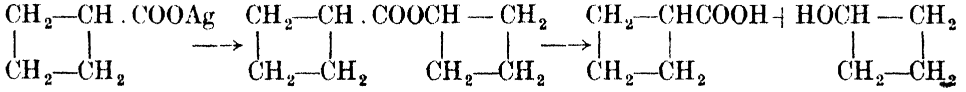


(117)



(118)

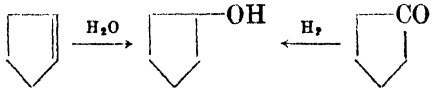
allyl alcohol or propanol are isolated when processes calculated to produce the cyclic alcohol are carried out. On the other hand, *cyclo*butanol (118) can be obtained by the action of nitrous acid on *cyclo*butylamine, or alternatively the silver salt of *cyclo*butane carboxylic acid is treated with iodine at 100°, when the following reaction takes place :—



(118*a*)

giving the ester (118*a*), which may be hydrolysed with the production of *cyclo*butanol. It is a liquid, b. 123°, which is readily oxidised to succinic acid by nitric acid, although with chromic acid an intermediate stage of *cyclo*butanone is recognisable. Passed over an alumina catalyst-mass, it is converted almost quantitatively to butadiene and water.

*Cyclo*pentanol, a liquid, b. 141°, is obtained easily by the reduction of the corresponding *cyclo*pentanone (119) by hydrogen when passed over an active nickel catalyst at 180°; another method is by the hydration of *cyclo*pentene (120) by Demjanov's method.[1]



(120) (119)

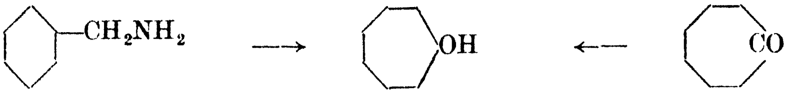
The main product of the nitric acid oxidation of *cyclo*pentanol is glutaric acid; some succinic acid is simultaneously produced.

*Cyclo*hexanol, is probably the most widely known member of this series; it is always obtained in quantity by the reduction of phenol by hydrogen in the presence of a suitable catalyst, usually some form of nickel. The reaction is almost quantitative, although some *cyclo*hexanone is produced. It is easier, in practice, to produce *cyclo*hexanone by catalytic reduction, and to submit this to a further reduction under suitable conditions. *Cyclo*Hexanol is a solid, m. 25° b. 161°, appreciably soluble in water and strongly hygroscopic. In general, little can be said of its chemical activity that is not summarised in the statement that it behaves as a secondary alcohol; oxidation leads to adipic acid, and when carried out catalytically with air is an industrial process of great value, giving a raw material for one of the nylons and also for a variety of other synthetic products.

---

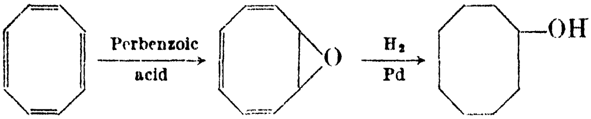
[1] Demjanov, *J. Soc. Phys. Chem. Russ.*, 1910, **42**, 850.

The preparation of *cyclo*heptanol (121) is accomplished either by the reduction of *cyclo*heptanone (suberone) with sodium amalgam or by the action of nitrous acid on hexahydro benzylamine,[1] an unusual example of an ' intrusive ' ring reaction :—



(121)

If *cyclo*octatetrene is converted to its epoxide by perbenzoic acid in cholroform, the epoxide can be substantially reduced to *cyclo*octanol by hydrogen in the presence of palladium :—



A variety of other cyclanols are known ; thus some *cyclo*propyl carbinol is produced in the conversion of *cyclo*butylamine to *cyclo*butanol by nitrous acid ; but no *cyclo*butyl carbinol is produced from *cyclo*pentylamine ; the former reaction is in opposition to that with benzylamine. In addition, there are alcohols of this series, homologous to *cyclo*hexanone, obtained by catalytic reduction of the cresols and xylenols, and Vavon [2] has investigated a wide variety of alkyl hexanols, both from the point of view of their preparation and from that of their stereo-isomerism.

Many of the higher members of the series are also terpene substances and, as such, are discussed in Chapter IX ; e.g. terpineol, menthol and pulegol.

THE PHENOLS

The simple phenols are among the most familiar of organic substances. Phenol itself was discovered by Runge [3] in 1834 from the fractionation of coal tar ; he called it " Kohlenölsaure "—which became translated as " carbolic acid ", although Laurent in 1841 named it " phenyl hydrate " or " phenic acid ", whence is derived its systematic name. Gerhardt coined the name ' phenol ' realising that phenol is a kind of alcohol. The fact that phenol could be easily obtained from coal-tar led to its manufacture in bulk as early as 1860 at Offenbach by Sell, and at Frankfürt by Brönner. In this country the manufacture of phenol was undertaken by Crace Calvert and Lowe (later Crace Calvert and Thompson) near Manchester, in 1861. It was not until 1867 that Lister drew attention to its antiseptic properties, which were, apparently, suggested to him by the analogy with creosote (the derivation of the word ' creosote ' is an allusion to the flesh-preserving qualities of the substance).

Many phenolic substances occur naturally ; thymol is a comparatively simple example, and carvacrol, eugenol, guaiacol and a host of others are to be found in plants. Traces of phenol itself occur in animal fluids, and urine may contain up to 1 per cent.

Much of the phenols, cresols and xylenols of industry arises from the distillation of coal ; low temperature tars have often over 40 per cent. of phenols, and such tars will undoubtedly come into prominence shortly, when low temperature pithead carbonisation becomes an accomplished fact. Ordinary coal-tar contains less phenols than the low temperature tar, but the proportion is still considerable, and for many years coal-tar was the main source of such substances; the demand for phenols, however, caused by the development of the plastics industry, has led to a position in which the coal-tar industry cannot supply the whole requirements of industry and supplementary phenol has to be produced by synthetic means.

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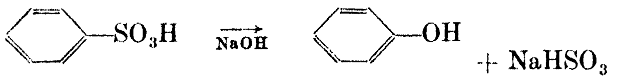
[1] Willstätter, *Ann.*, 1901, **317**, 218.

[2] Vavon. See a series of papers in *Bull. Soc.*, 1926-1932.

[3] Runge, *Pogg. Ann.*, 1834, **31**, 65 ; **32**, 308.

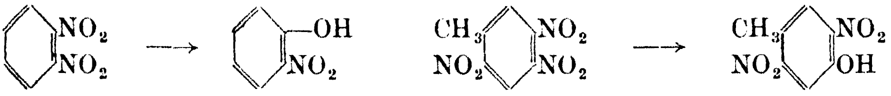
The general methods for introducing the phenolic hydroxyl into an aromatic nucleus are as follows:—

(1) Caustic fusion of the sulphonic acid:—



This process can be used for monohydric, dihydric and some trihydric phenols, and is the basis of one industrial method for converting benzene to phenol. The difficulty of obtaining sufficiently economical utilisation of sulphuric acid in this process is one reason for the intensive research which has been directed towards the production of benzene-sulphonic acid; vapour phase sulphonation of benzene in which the vapour of the hydrocarbon is passed through hot sulphuric acid at a temperature too high to allow of retention of the water formed appears to be one form of solution of this aspect of phenol manufacture.

(2) A nitro group can, if sufficiently activated by the presence of other 'acid' groups, be replaced by hydroxyl either directly or indirectly. Thus, *o*-dinitrobenzene is converted to *o*-nitrophenol (122); the same behaviour is



(122) (123) (124)

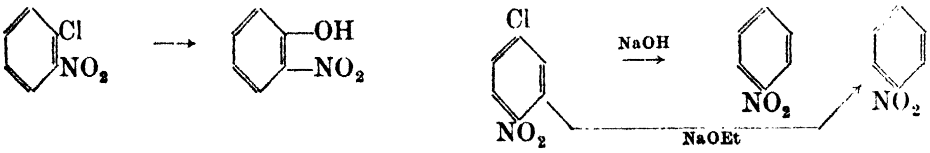
observed with unsymmetrical trinitrotoluene (123), which gives some dinitro-*p*-cresol (124) on treatment with alkali.

(3) If chlorobenzene be heated with 15 per cent. soda solution in the presence of copper at 300° for twenty hours,[1] an almost theoretical conversion to phenol is obtained:—

$$C_6H_5Cl + NaOH \longrightarrow C_6H_5OH + NaCl$$

This reaction has been suggested as an industrial method for the preparation of phenol, but the wasteful use of chlorine (1 kg. for each kg. of phenol produced) makes the process normally uneconomic.

When the benzene ring contains 'acid' substituents, the reaction proceeds more easily. Thus, *o*- and *p*-chloro nitro benzenes give *o*- and *p*- nitrophenol in good yield when heated under pressure with dilute alkalies:—



and by using sodium hydroxide in 60 per cent. ethanol the reaction can be extended to obtain good yields of *o*-nitrophenetole. Even the presence of two halogens serves to increase the ease of their removal. Thus symmetrical dibromotoluene (125) yields orcinol on alkaline fusion :—

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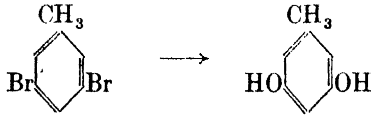
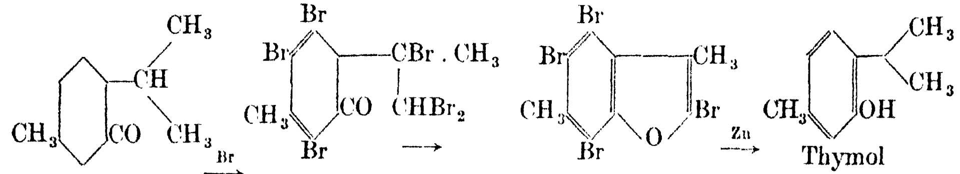
[1] Meyer and Bergous, *Ber.*, 1914, **47**, 3155.



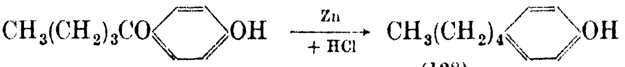
(125)

(4) Oxidation of cyclanols frequently gives phenols; thus menthol gives thymol; camphor gives carvacrol, and nearly all terpene alcohols and ketones yield some phenolic body on oxidation under suitable conditions. The transformation of menthone (126) to tetrabromo dimethyl coumaron (127) on oxidation with bromine, and the reduction of the coumaron to thymol[1] is shown thus

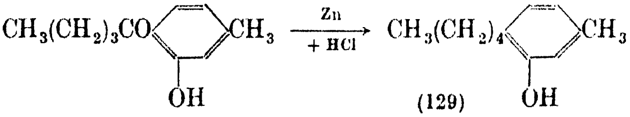


Menthone (126) (127)

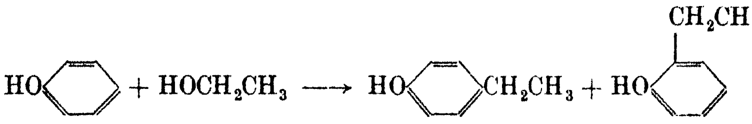
(5) Acetyl phenols, or acyl phenol ethers are reduced easily, and often nearly quantitatively to the corresponding alkyl phenols. Thus, *p*-*n*-valeryl phenol is reduced by zinc and hydrochloric acid to *p*-*n*-amylphenol (128). The reaction has proved valuable in the development of phenols, such as amyl-*m*-cresol (129).



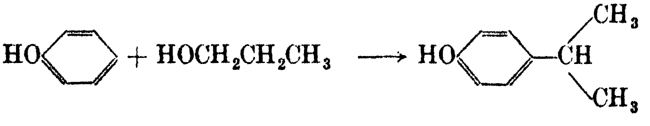
(128)

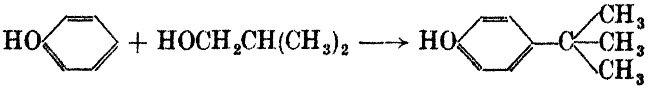


(6) The homologues of phenol may be prepared by condensing that substance with an aliphatic alcohol in the presence of zinc chloride, sulphuric acid, or an alkaline bisulphite. The *p*-isomer preponderates over the ortho-compound formed at the same time :—



The course taken by this reaction is very reminiscent of that of the Friedel-Crafts reaction; *n*-alcohols give *iso* or *tertiary* alkyl phenols, and *iso*-butanol gives tertiary butyl derivatives :—





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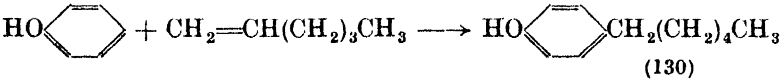
[1] Baeyer and Seuffert, *Ber.*, 1901, **34**, 40.

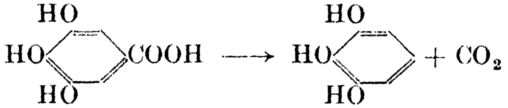
(7) Probably the best method of obtaining alkyl phenols is by passing the appropriate alkylene into a solution of phenol in one part of sulphuric and nine parts of acetic acid. Thus, ethylene gives the ethyl phenols, propylene propyl and *iso*-propyl phenols. Hexene-1 gives a considerable proportion of hexyl phenol (130) :—



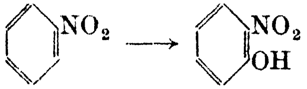
(130)

The amount of *o*-isomer produced appears to decrease with the increase in size of the entering group.

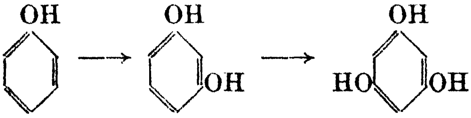
(8) It is, of course, often possible to obtain a phenol by dealkylation of its ethers ; thus anisole or phenetole give phenol on heating with concentrated hydriodic acid. In addition, some phenolic acids lose carbon dioxide on heating to give the phenol. This is particularly valuable in the production of pyrogallol by the action of heat on gallic acid :—



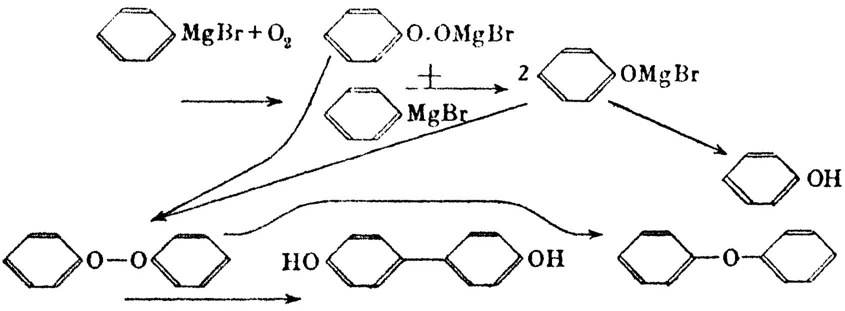
(9) The reaction $C_6H_5 + O \longrightarrow C_6H_5OH$ is possible ; Friedel and Crafts observed it in their early researches [1] when oxygen was passed through a stirred suspension of anhydrous aluminium chloride in benzene. The yield is poor. Other oxidising agents—ozone, hydrogen peroxide, give similar results. It is only when certain acid groups are present in the molecule that the reaction becomes of practical importance. Thus, nitrobenzene gives a 45-50 per cent. yield of *o*-nitrophenol when heated in potash suspension :—



A similar reaction takes place when phenols are fused with caustic soda, a di- or trihydric phenol being obtained by oxidation. Thus phenol gives resorcinol and phloroglucinol :—



(10) Phenol is produced, among other products, when a solution of phenyl magnesium bromide is oxidised. Some of the reactions are set out in the scheme below :—



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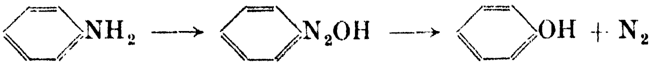
[1] Friedel and Crafts, *C.R.*, 1878, **86**, 884.

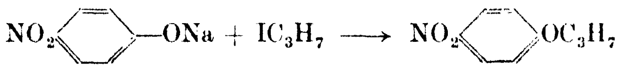
(11) It is, of course, possible to prepare phenols by the loss of nitrogen from a diazonium compound. The reaction is a valuable synthetic method, but is not used for large-scale production.



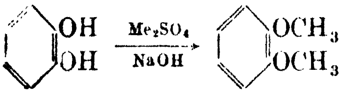
Phenolic Properties

Phenols differ in their acidic properties from alcohols, being able to exhibit an acid reaction to indicators and to react with solutions of bases to form salts, which are, however, easily dissociated. They are decomposed by carbon dioxide, although when dry and heated to 100° they react with carbon dioxide to form phenyl sodium carbonate, $C_6H_5O \cdot COONa$. The strength of the phenolic acid properties is enhanced by the presence of nitro- or halogen substituents in the ring; thus, nitrophenols and chlorophenols are stronger acids than phenol.

The hydroxyl group of phenols is readily alkylated by the use of the sodium salt and an alkyl iodide, as with p-nitrophenol propyl ether (131); for methylation, dimethyl sulphate is available in the presence of alkali (132), and the recent manufacture of diethyl sulphate in bulk makes the corresponding ethylation equally easy.



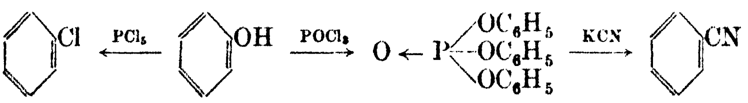
(131)



(132)

Esters of phenols are readily obtained; in many cases the acid chloride is used as the acylating agent; but acetic anhydride in pyridine, with a trace of sulphuric acid in the capacity of a catalyst, is probably the best and most widely used reagent for the purpose.

The hydroxyl group of phenols may be replaced by a variety of groups; the use of phosphorus pentachloride leads to replacement by chlorine, although the use of phosphorus oxychloride gives triphenyl phosphate, a valuable paint and varnish intermediate (133):—



(133) (134)

The triphenyl phosphate reacts very smoothly with potassium cyanide to give the nitrile (134). Phosphorus pentasulphide converts phenols to thiophenols; and ammonia replaces the hydroxyl by the amino group. Thus, phloroglucinol in ammoniacal solution deposits crystals of phloramine (3, 5-dihydroxy aniline).

The higher phenols and naphthols give good yields of amino-compounds when submitted to the action of ammonia and sulphites (Bucherer's reaction).[1] The reverse change is used also for converting amines to phenols. The industrial production of β-naphthylamine from β-naphthol and ammonia in the presence of sulphites is an instance of the application of Bucherer's reaction.

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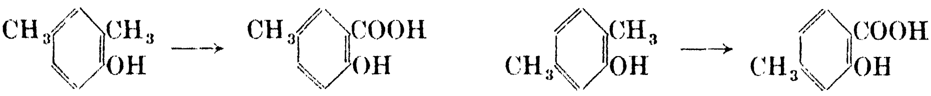
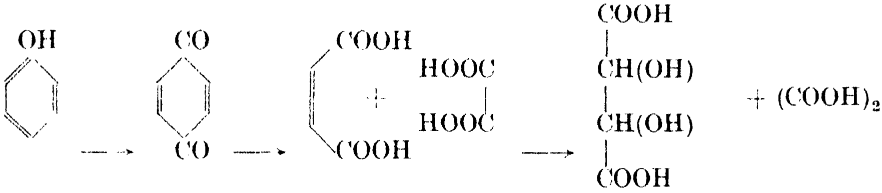
[1] Bucherer, *J. Pr. Chem.*, 1904, (2), **69**, 88.

The reaction of ammonia with simple phenols is best carried out by the use of ammonia-zinc chloride which gives a higher yield (up to 75 per cent. of the theoretical quantity). The oxidation of alkyl side-chains in phenols is of interest. Thus, the cresols on oxidation give hydroxy benzoic acids; the xylenols and thymol, which contain two alkyl side-chains attached to the nucleus, are capable of giving not only the dicarboxylic acids on oxidation, but also, by the use of milder reagents, a monocarboxylic acid. As it is nearly always the alkyl group adjacent to the hydroxyl which is oxidised to carboxyl, some otherwise unavailable cresotinic acids can be obtained, *e.g.* *as*-*m*-xylenol gives 3-methyl-6-hydroxybenzoic acid (135); *p*-xylenol (136) gives 4-methyl-2-hydroxybenzoic acid (137).



(135) (136) (137)

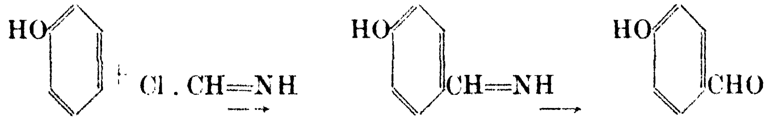
If phenol itself be submitted to strenuous oxidation by permanganate, meso-tartaric acid is obtained, although the yield is not good. The course by which this acid is obtained is probably as indicated below:—



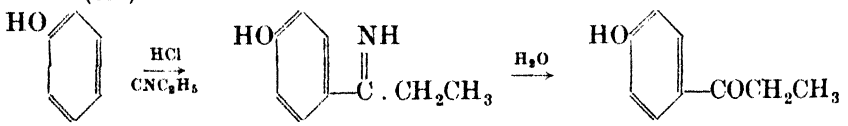
Phenols are readily halogenated (see p. 311), and equally easily nitrated and nitrosated (see Chap. I, Vol. II); it is undoubtedly true that the presence of a hydroxyl group in the ring makes the nucleus much more susceptible to the attack of reagents since, in general, the phenols are far more reactive than the corresponding hydrocarbons.

The remaining reactions of phenol are summarised under the following headings, since many of them will be dealt with in detail under a specific group later in this book.

(1) *Formation of Phenolic Aldehydes.*—Neither Étard's chromyl chloride reaction, nor the formyl chloride Friedel-Crafts reaction is satisfactory for the introduction of the aldehyde group into phenols, so that the Gattermann reaction with hydrochloric and hydrocyanic acids is used (138); an imine is formed which reacts readily with dilute acids to give the phenolic aldehyde;



(138)



(139) (140)

aryl and alkyl nitriles can be used in a similar reaction in which ketones are formed as in (139) and (140). The formation of the aldehydes of this series can also be accomplished by the reactions of Reimer and Tiemann,[1] in which chloroform and phenol are allowed to react in the presence of alkali. The course of the reaction appears to be as follows :—

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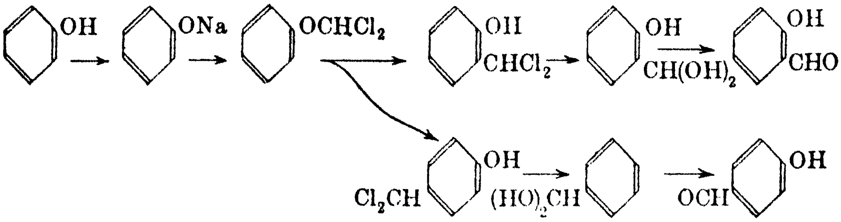
[1] Reimer and Tiemann, *Ber.*, 1876, **9**, 824, 1268; 1878, **11**, 770.



Both *o*- and *p*-hydroxy benzaldehyde are formed. The replacement of the chloroform by trichloroacetic acid improves the yield of aldehydes considerably. The Tiemann-Reimer reaction is of no value for introducing the aldehyde group into polyhydroxy phenols. Methylene chloride or carbon tetrachloride in place of the chloroform yield benzyl alcohols or benzoic acids respectively.

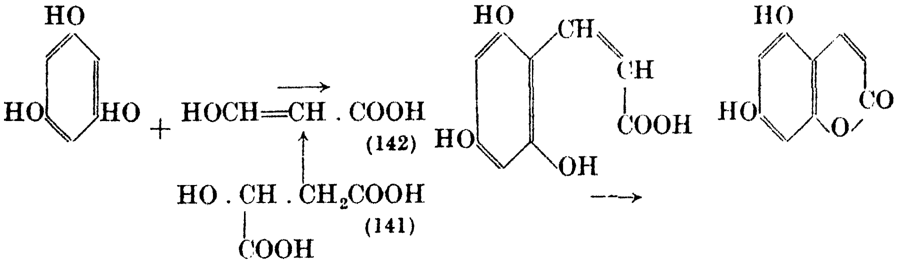
(2) *Coupling Reactions.*—Diazonium salts couple readily with phenols, another example of the enhanced reactivity of the phenolic ring ; the compounds obtained are often highly coloured, and form many of the azo-dyes of commerce. If the position *para* to the hydroxyl group is free, coupling almost invariably takes place at this point ; failing this the positions *ortho-* to the hydroxyl are the seat of coupling ; from phenol itself 2, 4, 6-*tris* azo compounds are obtainable.

(3) Isocyanates and thiocarbimides react with phenols to give the carbamic and thiocarbamic esters :—

$$C_6H_5OH + OCN\,.\,C_6H_5 \longrightarrow C_6H_5O\,.\,CO\,.\,NH\,.\,C_6H_5$$
$$C_6H_5OH + SCN\,.\,C_6H_5 \longrightarrow C_6H_5O\,.\,CS\,.\,NH\,.\,C_6H_5$$

(4) The formation of naphthopyrylium bases from naphthols is discussed in Appendix IV to this chapter.

(5) Phenols condense directly with malic acid in the presence of sulphuric acid to give coumarins (alternatively prepared from *o*-phenolic aldehydes *via* the Perkin reaction).



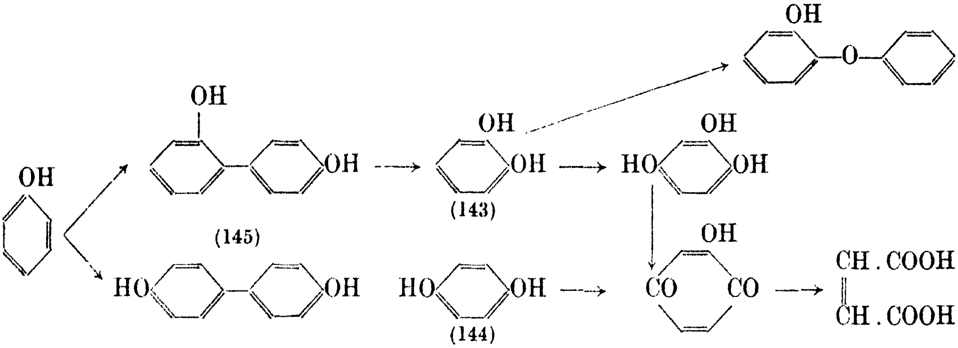
The malic acid (141) appears to react as though it had lost the elements of water and carbon dioxide to give formyl acetic acid (142). The reaction is a general one and capable of very wide application—to almost all phenols in which one position *ortho-* to the hydroxyl is free.

(6) The chemistry of the phthaleins, succineins and related compounds is discussed in Chapter XIII of Vol. II.

SOME INDIVIDUAL PHENOLS

The discovery and natural occurrence of phenol has already been mentioned. The recovery of phenol from the appropriate fraction of coal-tar (150-200°) is carried out by alkaline extraction ; the extract is treated with about 15 per cent. of the acid required completely to neutralise the alkalies, when much extraneous material is precipitated. The residual liquor is then precipitated with acid and the resultant oil dried and fractioned. The phenolic fraction is purified by freezing and partial thawing; phenol melts at 42-43° and boils at 181·3°.

The oxidation of phenol by reagents not sufficiently powerful to destroy it offers an intricate problem for solution. It appears that pyrocatechol and hydroquinone (143) and (144) are not the first products to be formed, but are the results of a long series of changes in which *p*, *p'* and *o*, *p'*-dihydroxy diphenyl (145) are involved. These dihydric phenols are again oxidised and, if moderately powerful oxidising agents are used, maleic acid is finally produced. These reactions are set out in the scheme below :—

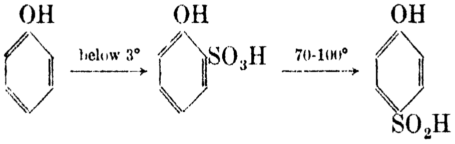


(143)

(145)

(144)

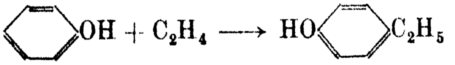
Sulphonation of phenol proceeds first to the *ortho*-sulphonic acid, which is produced almost exclusively if the solution is kept below 3°; on allowing the temperature to rise the *para* acid is produced by migration of the sulphuric group :—



The *o*-sulphonic acid is miscible with water in all proportions and is a useful antiseptic, milder in its action on the tissues than is phenol itself.

The nitration of phenol proceeds readily even in 20 per cent. nitric acid, to give a mixture of the *o*- and *p*-nitrophenols. Even with pure phenol a substantial portion is resinified, and whilst the *ortho* isomer can be removed almost quantitatively by distillation in steam, the *para*- isomer is difficult to separate from the resinous material; the formation of such resins can be eliminated by nitrating phenol in ethyl acetate solution, and alternative methods have been evolved for the production of the nitro-bodies from *o*- and *p*-chloronitrobenzene.

Phenol is a most reactive substance, and will react with unsaturated hydrocarbons in the presence of acetic and sulphuric acids. Thus ethylene can, under pressure, be induced to react with phenol to give ethyl phenol (146);



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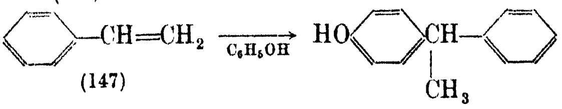

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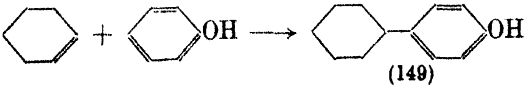
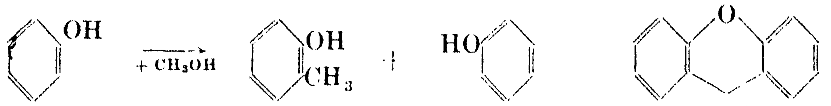
(148)



(149)

Styrene (147) reacts with phenol to give a 4-hydroxydiphenylethane (148) and *cyclo*hexene yields 4-*cyclo*hexylphenol (149); in the latter case both diphenyl oxide and di*cyclo*hexyl oxide are also formed.

The action of methanol on phenol in the presence of alumina at 400° and a pressure of 200 atmospheres, gives almost entirely *o*-cresol, with a little xanthene (150).

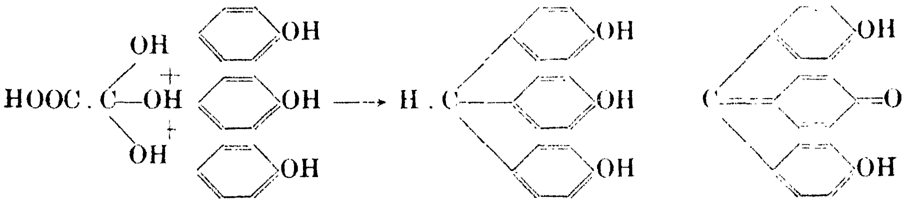


(150)

If the temperature and pressure be increased, the whole of the phenol (provided the requisite amount of methanol be present) is converted to hexamethyl benzene.

If ethanol is allowed to react with phenol in the presence of anhydrous aluminium chloride, some *p*-ethyl phenol can be isolated; but the yield is greater when ether is used in place of ethanol.

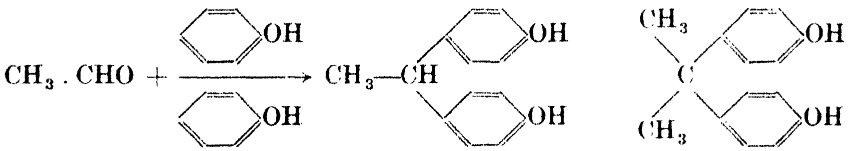
It has already been mentioned that, by an extension of the Tiemann-Reimer reaction, phenol reacts with carbon tetrachloride to yield *p*-hydroxy benzoic acid; if the condensation of these reactants takes place in the presence of zinc chloride, an entirely different course of reaction is observed, both aurin and leucaurin are obtained, together with other products :—



(151) Leucaurin Aurin (*p*-rosolic acid)

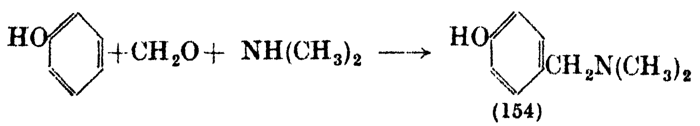
Aurin and leucaurin are much more easily obtained by heating phenol with oxalic and sulphuric acids (151). The aurins are described more fully in Chapter XIII, Vol. II.

The condensation of phenol and formaldehyde is discussed in Appendix III in relation to 'Plastics', but it may be added here that phenol is capable of reacting with almost every aldehyde or ketone, through the labile hydrogen in the *p*-position, e.g. with acetaldehyde, *p*, *p*′-dihydroxy-1, 1 diphenyl ethane



(152) (153)

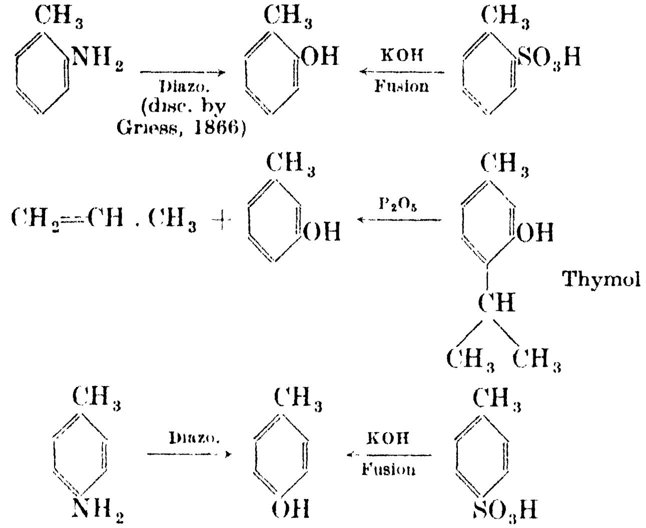
is obtained (152), and with acetone the corresponding *p*, *p*′-dihydroxy-2, 2 diphenyl propane (153) is the product. The interaction of phenol, formaldehyde and dimethylamine to give dimethylaminomethyl phenol (154) is an interesting extension of this reaction.



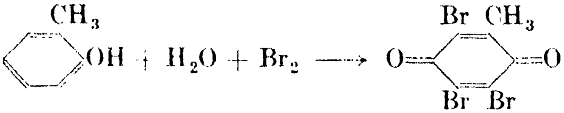
(154)

THE CRESOLS

The existence of a homologue of phenol in cow's urine was proved by Städeler[1] in 1851; he called the new acid 'taurylic acid'; Fairlie[2] obtained what he termed 'hydrate of cresyl' from coal-tar creosote, but it remained for Engelhardt and Latschinov[3] to discover the existence of three isomeric cresols which they obtained by reactions set out in the scheme below:—

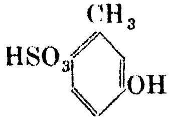


o-Cresol is capable of being separated from the crude cresylic acid fraction of the tar acids by careful distillation. It forms a solid crystalline mass m. 30·1° and b. 191°. The reactions of *o*-cresol resemble those of phenol, except that the direct action of bromine upon it is to give tribromotoluquinone (155) by simultaneous oxidation and bromination:—



(155)

m-Cresol.—The residue after the fractionation of *o*-cresol contains *m*- and *p*-cresols in proportion of 3 parts of the former to 2 of the latter. Simple physical methods are insufficient to separate these two isomers, and a large variety of chemical means have been proposed in order to obtain comparatively pure *m*- and *p*-cresols. Of these the sulphonic acid, acetate and urea processes are probably the most satisfactory and widely used. In the sulphonation processes the mixed cresols are converted to the sulphonic acids (156) and (157) by warming



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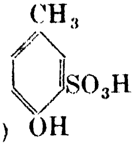

(157)

with just under their weight of 94 per cent. sulphuric acid. On cooling a mass of crystals of the *p*-cresol sulphonic acid separates, and can be centrifuged from the mother liquor which is rich in the *m*-acid. Distillation with superheated steam reconverts the sulphonic acids to their cresols and furnishes a comparatively pure *p*-cresol, with a *m*-cresol of about 80 per cent. purity. By taking advantage of the fact that the *m*-cresol sulphonic acid is decomposed by superheated steam at 125°, whilst the *para*-acid requires a temperature of 160°, further enrichment can be attained.

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[1] Städeler, *Ann.*, 1851, **77**, 188.

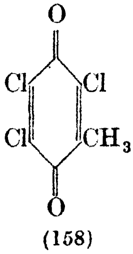
[2] Fairlie, *J.C.S.*, 1853, **7**, 232.

[3] Engelhardt and Latschinov, *Zeitschr. Chem.*, 1869, 618.

In the acetate process as developed by Monsanto, the *m*- and *p*-cresols are treated with a solution of sodium acetate in solvent naphtha when the double compound with *m*-cresol separates alone; after washing it may be heated with solvent naphtha, when the addition compound is broken down to sodium acetate and *m*-cresol, the latter being recovered from the solution at 98-100 per cent. partly by fractional distillation. This leaves a *p*-cresol-rich solution in solvent naphtha which on agitation with anhydrous oxalic acid gives a *p*-cresyl compound separating in crystals, from which *p*-cresol may be isolated in a state of purity.

In the urea process equimolecular proportions of the mixed cresols and urea are warmed to 70° when the heat of reaction takes the temperature up to 120° and a clear solution is obtained. Cooling is allowed to take place until the first crystals appear, at which point petroleum spirit (boiling range 120-150°) is added with stirring and the cooling coils turned on, using brine. Stirring is continued until the temperature reaches 0°, when a brei of crystals and liquid is obtained; the crystals, which are separated by centrifuge, are a compound of *m*-cresol and urea; it can be decomposed by warm water when the *m*-cresol separates as an oily layer above the concentrated urea solution. Purified by vacuum distillation, it contains 97-100 per cent. of *m*-cresol. The *p*-cresol remaining in the petroleum spirit is recovered by the oxalic acid process described above.

m-Cresol is liquid at ordinary temperatures; pure specimens melt at 4° and boil at 202-203°, whilst chlorine oxidises *m*-cresol to trichlorotoluquinone (158), bromine gives the tri-bromo compound normally (159). *Iso*-propyl and *sec*-butyl alcohols when heated to 200° with *m*-cresol and anhydrous magnesium chloride give the *o*- and *p*- *iso*-propyl and *sec*-butyl derivatives (160) and (161). An interesting reaction of *m*-cresol is with trimethylene chlorhydrin;



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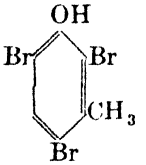

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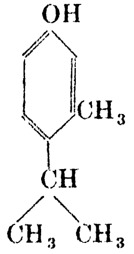

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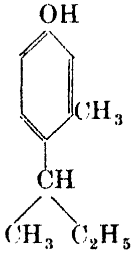

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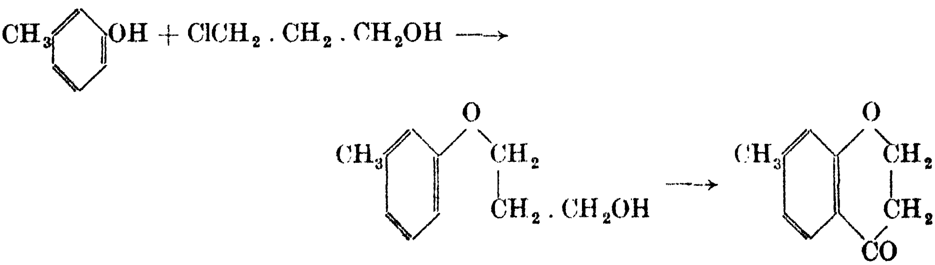
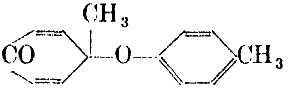


(162) (163)

3 (3-methyl phenoxy) propanol (162) is obtained which, on oxidation with acid or neutral permanganate, followed by dehydration of the acid so obtained, yields 7-methylchromanone (163), a liquid with a pleasant smell of citron.

p-Cresol, the formation of which has already been described, is a white solid resembling phenol in appearance and odour; it has a sharper smell, however, and is a more powerful bactericide (m. 35-36°, b. 202°).

In some respects the reactions of *p*-cresol differ from those of its two isomers; thus, on oxidation with ferricyanide a keto-diphenyl oxide derivative (164) is obtained, which gives a normal oxime, semicarbazone and phenylhydrazone.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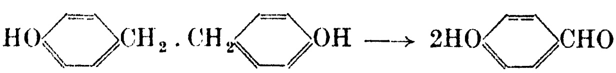
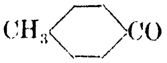

(165)

When oxidised with persulphates (in neutral solution) *p*-cresol is converted to 4, 4′-dihydroxy dibenzyl (165); in acid solution the dibenzyl derivative is not isolated, but passes into the aldehyde (cf. oxidation of dibenzyl to benzaldehyde, Chap. VI). The reduction of *p*-cresol can be controlled to give either the methyl *cyclo*-hexanone (166) or the methyl *cyclo*-hexanol[1]; to obtain the former,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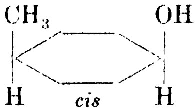
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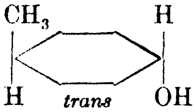
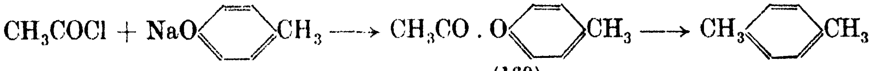
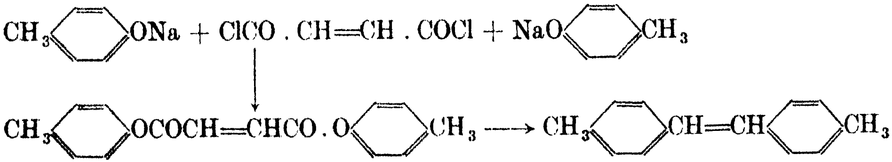

(168)

p-cresol is reduced by hydrogen in the presence of finely divided platinum and of semicarbazide hydrochloride, the semicarbazone of methyl *cyclo*-hexanone separating as fast as formed. The reduction carried out on *p*-cresol in an emulsion with gum arabic yields, in the presence of acetic acid and at a temperature af 70°, the *cis*-methyl *cyclo*-hexanol (167); at 10° and in neutral suspension the *trans*-isomer is obtained (168).

The lability of the hydroxyl group in *p*-cresol is nowhere more apparent than in the condensation which it undergoes with acid chlorides. Thus, with acetyl chloride, reaction takes place readily to give acetyl-*p*-cresol (169), and this on heating decomposes, giving some *p*-xylene; the yield in this case is


(169)

poor, but in the case of fumaryl chloride reasonable yields of dimethylstilbene (170) are obtained, and the reaction is of synthetic importance.


(170)

The Xylenols

All six xylenols can be obtained from coal-tar phenolic fractions, although in some cases the separation is extremely tedious. The xylenol fraction of the tar acids, from 206-224° is usually split into two fractions, 206-217° and 217-222°, the latter containing the bulk of the *s*-*m*-xylenol; in low temperature tars this is a very large fraction from which considerable supplies of 3, 5-xylenol are obtained industrially by Kester's method. The 217-222° fraction is recrystallised from petroleum spirit (low boiling) from which pure 3, 5-xylenol separates; the residue from the ether crystallisation, after removal of the solvent, is treated with 26 per cent. caustic soda, when the sodium salt of 3, 5-xylenol separates; alternatively, the residue of crude 3, 5-xylenol from the first crystallisation can be distilled and monochlorinated to give powerful antiseptics of the 'Cresantol' class. The physical characteristics of the xylenols are given in Table VI, together with those of some of the higher methyl phenols, the reactions of which it is unnecessary to particularise.

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[1] Berton and Vavon, *Bull. Soc. Chim.*, 1923, **33**, 538.

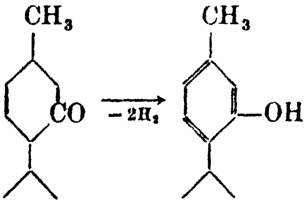
TABLE VI

SOME HIGHER PHENOLS

Name	Structure	M.P.	B.P.	Other properties
1, 2, 3-Xylenol .	$(CH_3)_2C_6H_3 . OH$ (1, 2, 3)	73°	213°	d_{15} 1·034
1, 2, 4-Xylenol .	$(CH_3)_2C_6H_8 . OH$ (1, 2, 4)	65°	222°	
1, 3, 2-Xylenol .	$(CH_3)_2C_6H_3 . OH$ (1, 3, 2)	49°	203°	
1, 3, 4-Xylenol .	$(CH_3)_2C_6H_3 . OH$ (1, 3, 4)	25°	209°	d_{20} 1·036
1, 3, 5-Xylenol .	$(CH_3)_2C_6H_3 . OH$ (1, 3, 5)	64°	220°	
1, 4, 2-Xylenol .	$(CH_3)_2C_6H_3 . OH$ (1, 4, 2)	75°	209°	d_{10} 0·971
ψ-Cumenol . .	$(CH_3)_3C_6H_2 . OH$ (1, 2, 4, 5)	73°	234-235°	
Hemimellitol .	$(CH_2)_3C_6H_2 . OH$ (1, 2, 3, 5)	81°		
Mesitol . . .	$(CH_3)_3C_6H_2 . OH$ (1, 3, 5, 2)	70-71°	220°	
Prehnitol . .	$(CH_3)_4C_6H . OH$ (1, 2, 3, 4, 5)	86-87°	266°	
Durol . . .	$(CH_3)_4C_6H . OH$ (1, 2, 4, 5, 3)	117°	250°	
Pentamethylphenol	$(CH_3)_5C_6 . OH$	125°	267°	
o-Ethylphenol .	$C_2H_5 . C_6H_4OH$ (1, 2)		203°	
m-Ethylphenol .	$C_2H_5 . C_6H_4OH$ (1, 3)		214°	
p-Ethylphenol .	$C_2H_5 . C_6H_4OH$ (1, 4)		219	
p-*n*-Propylphenol .	$C_3H_7 . C_6H_4OH$ (1, 4)		232°	d 1·009
p-*iso*-Propylphenol	$(CH_3)_2CH . C_6H_4 . OH$ (1, 4)	61°	229°	
p-*ter*-Butylphenol .	$(CH_3)_3C . C_6H_4 . OH$ (1, 4)	90°	238°	d_{15}0·908
p-*ter*-Amylphenol .	$(CH_3)_2(C_2H_5)C . C_6H_4OH$ (1, 4)	94°	266°	
Thymol . .	$(CH_3)_2CH . C_6H_3(CH_3)OH$. (4, 1, 3)	51·5°	233·5°	
Carvacrol . .	$(CH_3)_2CH . C_6H_3(CH_3)OH$. (4, 1, 2)	+ 0·5°	238°	

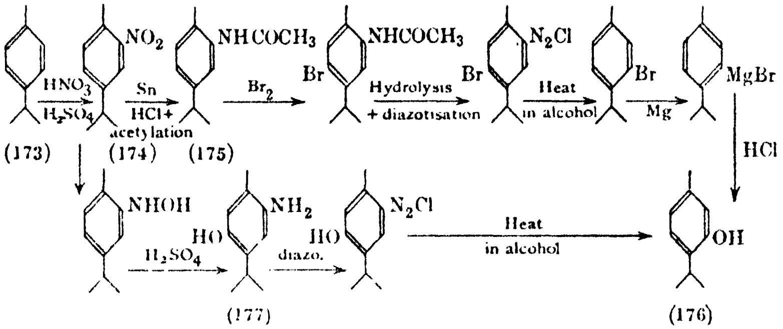
Thymol, one of the oldest known members of the phenol group, was observed as a deposit in oil of thyme, and was for a long time known in England as "sal volatile thymis" before the Berlin apothecary, Neumann, observed it in 1719; it has been known from time immemorial in India as 'flowers of Ajowan'. It has been isolated from many essential oils, and is characterised by a very pleasant odour, and a powerful antiseptic action.

Many syntheses of thymol have been devised; the most practical method of obtaining thymol is the transformation of menthone (171) by heating with



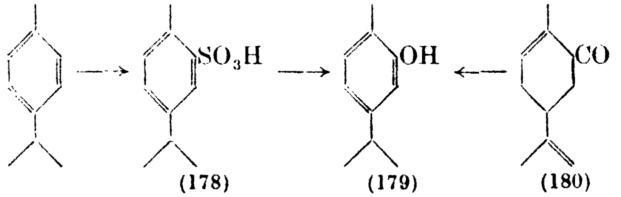
(171) (172)

sodium to 350°, when hydrogen is evolved (172). Menthol may be used in place of menthone, but is usually less readily available. Much thymol is prepared from Ajowan oil. Many syntheses of thymol have been described which indicate its constitution. Thus, cymene can be nitrated, reduced to amino-cymene (173), and by the usual methods converted to thymol, as indicated in the



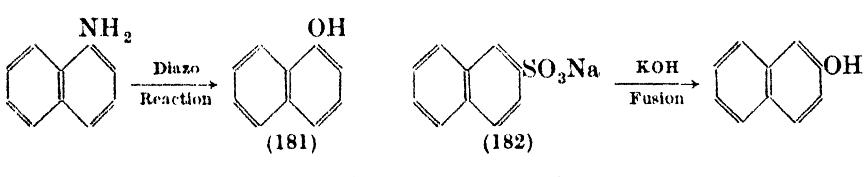
formulæ (173 to 176). It is, however, more expeditious to reduce nitro-cymene electrolytically in sulphuric acid solution, where it passes through the hydroxylamine stage to amino-thymol (177), and by diazotisation and heating in alcoholic solution may be converted to thymol (176).

Carvacrol constitutes about 80 per cent. of origanum oil, from which it can be extracted by aqueous alkalies, followed by precipitation and fractionation. It may be prepared by the direct sulphonation of cymene, followed by



caustic fusion of the sulphonic acid (178) to give carvacrol (179). It may also be obtained directly from carvone (180) by heating the latter with phosphoric, formic or sulphuric acids. The change involves numerous stages.

The fused ring phenols, naphthols, phenanthrols and their analogues constitute a very important group of substances. It is proposed to deal first with the naphthols. α-Naphthol (181) was the first to be prepared, and was



obtained by Griess[1] in 1867 by the diazotisation of α-naphthylamine. The best method of preparing pure α-naphthol is to heat α-naphthylamine with 45 per cent. sulphuric acid under pressure for 8 hours at 200°, a pressure of 15-16 atmospheres being developed. On cooling, the α-naphthol is separated from the ammonium sulphate liquor and distilled in a good vacuum. α-Naphthol can also be prepared in a grade suitable for some industrial purposes by the caustic fusion of sodium naphthalene α-sulphonate, but the marked tendency of the sulphonic group to migrate to the β-position means that the product will be contaminated with β-naphthol. α-Naphthol forms brilliant needles, m. 94°, b. 280°. It is only slightly soluble in water, but readily forms a soluble sodium salt. Like phenol, it has antiseptic powers, and in general it may be said that the naphthols are true phenols in their chemical behaviour, although the hydroxyl group of the naphthols is more labile and reacts, for example, with ammonia to give the corresponding amine quite readily.

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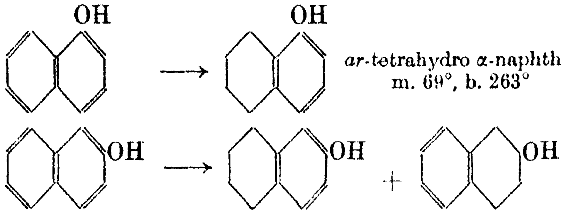
[1] Griess, *J.C.S.*, 1867, **20**, 89.

β-Naphthol, which crystallises in plates, m. 122°, b. 286°, is always prepared by the caustic fusion of sodium naphthalene-β-sulphonate (182), and after separation, is distilled in vacuum. It is widely used for the preparation of azo-dyes, and as a developer in calico printing.

The naphthols are interesting in respect of their reduction to tetrahydro bodies; reduced with sodium and alcohol, α-naphthol gives exclusively the ar-tetrahydro compound, whilst β-naphthol under similar circumstances yields a mixture of ac- and ar- tetrahydro β-naphthols in which the former predominates. Whilst the ar- tetrahydro naphthols are entirely phenolic in character, the ac- isomers behave as aliphatic secondary alcohols and may, for example, be oxidised to the cyclic ketones.

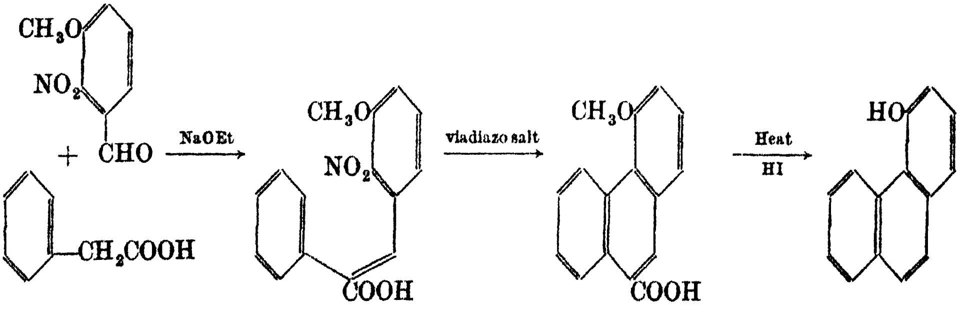


ar-tetrahydro α-naphthol
m. 69°, b. 263°

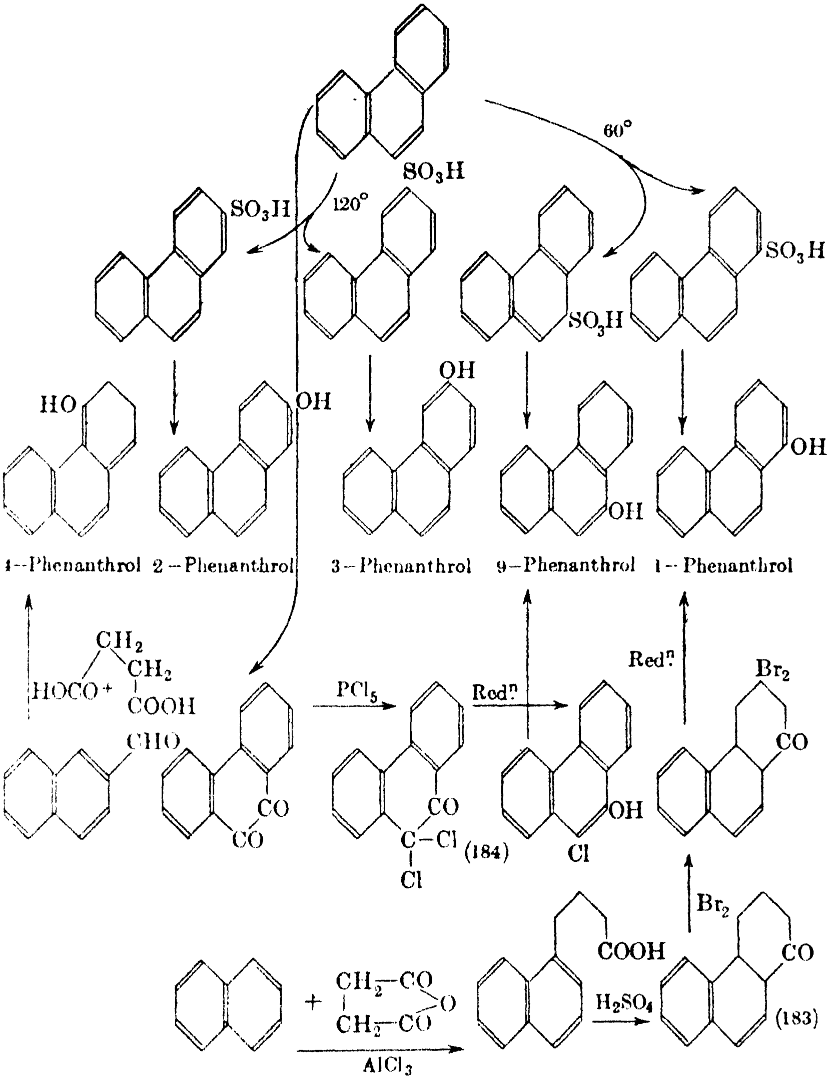
ar- *ac*-
tetrahydro β-naphthol
m. 59°; b. 276° b. 262°

All five phenanthrols are known, and their preparation is indicated in the scheme on the opposite page.

The sulphonation of phenanthrene at 120° yields up to 30 per cent. of each of the 2- and 3-sulphonic acids, with little 1- or 9-acid. The remainder of the phenanthrene is converted to disulphonic acids. At 60° appreciable quantities of 1- or 9-sulphonic acids are obtainable (about 15 per cent. of the 9- and 10 per cent. of the 1-acid), but are difficult to separate from the other products. Thus, although all four acids yield the corresponding phenanthrol on caustic fusion, only the 2- and 3-phenanthrols are conveniently obtained by this means. 1-Phenanthrol is obtained by using Haworth's method to obtain 1-keto tetrahydrophenanthrene (183), which on bromination yields a dibromide; the latter on boiling with dimethylaniline loses the elements of hydrogen bromide, and gives 1-phenanthrol. 9-Phenanthrol is made from phenanthrene quinone by conversion to the dichloro compound (184). Reduction of the latter with a saturated solution of stannous chloride in glacial acetic acid containing hydrogen chloride yields 9-phenanthrol. 4-Phenanthrol is difficult to obtain; the condensation of succinic acid with β-naphthaldehyde has been used for its preparation, but the yield is poor. It is probably easier to obtain 4-phenanthrol through the methyl ether by Pschorr's method :—

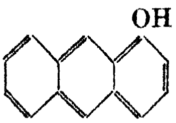


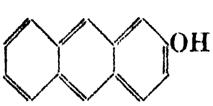
The drawback to this method lies in the inaccessibility of 2-nitro-3-methoxybenzaldehyde.

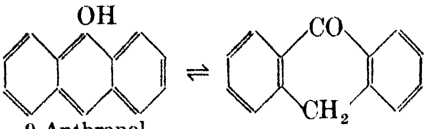


The Anthranols

Three anthranols, or hydroxyanthracenes, are theoretically possible; all have been prepared, but little is known of the 1- and 2-compounds. They can


1-Anthranol


2-Anthranol


9-Anthranol

Anthrone
(185)

be obtained by the caustic fusion of the anthracene sulphonic acids, and are solids with a peculiar odour; the α-form (1-anthranol) has m. 153°, but the β- or 2-anthranol decomposes about 200°. They have a very marked tendency to pass by oxidation into the corresponding hydroxyanthraquinone (see Chap. VI). 9-Anthranol, often referred to as 'anthranol', is a valuable intermediate in the production of benzanthrones, used industrially for the manufacture of Indanthrene dyes (*q.v.*). It is obtained by dissolving anthraquinone in concentrated sulphuric acid and reducing to anthranol with aluminium dust; on pouring into water anthranol separates; it changes readily, even on storage alone, to anthrone (185), m. 154°. The distinction between anthrone and 9-anthranol can be most easily made by examination with a U.V. source; anthranol is fluorescent, whilst anthrone is not. The conversion of anthrone to anthranol is carried out by solution in alkali and precipitation by cold dilute acid.

POLYHYDRIC PHENOLS

Of the simple dihydric phenols, orcinol was the first to be discovered by Robiquet [1] in 1829; he obtained it from a plant then known as *Lichen orcina* (now *Variolaria dealbata*) and this gave rise to the name.

The lichens, of the Rocella and Lecanora species particularly, have been used from very early times for the production of colouring matters for dyeing and other purposes. Outstanding amongst such colours are litmus and archil. Both are impure products, and both are obtained from the same lichens by different treatment. Litmus, one of the first reagents with which chemists become acquainted in their studies, is a mixture of substances of unknown constitution; even the derivation of the name is shrouded in mystery; the Continental word 'lackmus' may be derived from 'lacca musci' (a lake prepared from moss). Be that as it may, the Dutch appear to have been the first to use litmus, for the purpose of colouring their cheeses. The preparation of litmus involved pounding the lichens with carbonate of potash and allowing the mixture to stand in putrid urine; after a time the reddish-purple solution is treated with lime and potash and the whole mass allowed to dry off, when it forms the familiar blue pellets in which it is sold. A variety of litmus is obtained by allowing orcinol to stand with ammonia and sodium carbonate solution at 60-80° for a few days. On addition of hydrochloric acid a precipitate is obtained which in many ways resembles litmus but probably contains the various dyes of that commodity in different proportions. French or ribbon litmus is obtained in Southern France from the sap of *Croton tinctorium*, which is absorbed in clean waste rag and dried in the sun. On exposing the impregnated material on heaps of dung covered by straw, the pigment is formed as a result of the action of ammonia on the dried sap; the impregnation and sequential treatment is repeated until an accumulation of pigmented material has been built up; this preparation gives a brighter red than lichen litmus, and before the advent of synthetic dyes had taken the place of litmus in the Dutch cheese-making industry.

Archil is said to take its name from the Oricellari, a prominent Florentine family of the Middle Ages, who introduced the archil method of dyeing blues and purples from the Levant. The word is, however, of older origin than the family so named. The lichens were treated with stale urine and lime in large casks and the mixture was well stirred and allowed to stand for months, during which time the dye was formed. Later, a purified archil known as 'French purple' was obtained, and from this the dyestuff orceine has been isolated. In the light of the researches of Pavolino,[2] orceine appears to have the structure

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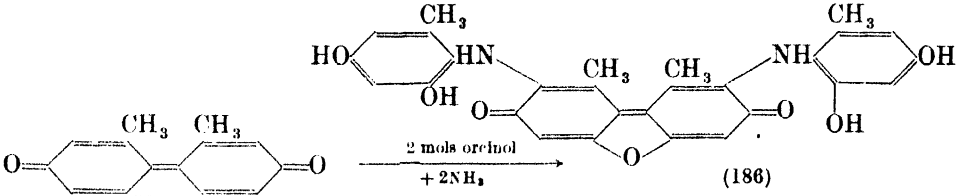
[1] Robiquet, *Ann. Chem. Phys.*, 1829, (2), **42**, 236.

[2] Pavolino, *Atti. IV. cong. naz. chim. pura applicata.* (1932), 1933, 557.

(186) in acid solution. The partial synthesis of orceine was achieved by the interaction of dihydroxy-4, 5-dimethyl diphenoquinone (187) and two mols. of orcinol. These substances are akin to those contained in cudbear, and used in the Scottish islands for tweed dyeing. It is easy to see how such substances, when boiled with milk of lime, yield orcinol.

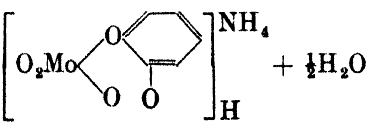


(187) (186)

The next dihydric phenol to be isolated was catechol (variously known as catechin, pyrocatechol and *o*-dihydroxybenzene), by Reinsch in 1839. Zwenger[1] made an examination of the substance, which was obtained by the dry distillation of catechin, and coined the name ' brenzcatechin '. Shortly after this, in 1844, Wöhler [2] observed that quinone was easily reduced to a colourless crystalline body, identical with that then recently obtained by Caventou and Pelletier by the pyrolysis of quinic acid. Wöhler called the new substance hydroquinone, an allusion to its method of formation. Last of the simple dihydric phenols to be discovered was resorcinol, isolated in 1864 [3] from the caustic fusion of galbanum resin. Its great similarity to the then well-known orcinol led to its being named ' resorcinol '.

Catechol.—Occurs widely in natural substances, either combined, as in the catechu tannins, or free as in the leaves of the Virginia creeper (*Ampelopsis hederaceæ*). Numerous synthetic methods are capable of yielding this phenol, such as the caustic fusion of *o*-iodo-, or *o*-bromo-phenol, or phenol-*o*- sulphonic acid. It was at one time obtained from beechwood creosote by demethylating the fraction distilling between 200-205° (mainly guaiacol) with hydriodic acid. It is best crystallised from benzene or from 1, 2, 4-xylenol. Industrially, catechol is now made by the alkaline fusion of *o*-dichlorobenzene, and is available in bulk quantities. It forms large crystals, m. 105°, b. 240°, which readily darken in air. It reduces silver salts in the cold, and, with a suitable restrainer, can be used as a photographic developer,

In chemical behaviour, catechol is a typical phenol ; it is characterised—as indeed are nearly all *o*-dihydroxy phenols—by the formation of an emerald green colour with ferric chloride solution. This is probably due partly to complex formation at the two hydroxyl groups ; catechol is able to form Werner complexes quite easily, and a series of highly coloured complexes of catechol with ammonium molybdate and cyclic bases has been studied. Thus, if catechol is dissolved in an ammoniacal solution of ammonium molybdate, large



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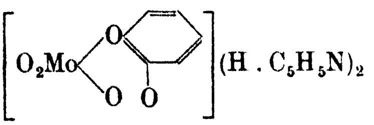

(189)

garnet red crystals of the compound (188) separate ; pyridine can take the place of ammonia, and with excess of it, complexes of the type (189) are formed.

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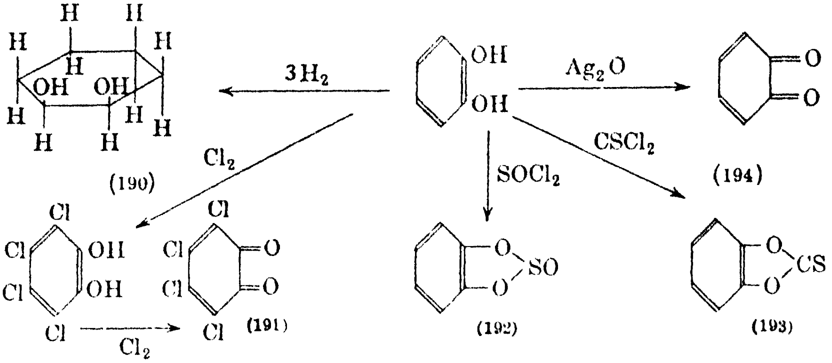
[1] Zwenger, *Ann.*, 1841, **37**, 327.

[2] Wöhler, *ibid.*, 1844, **51**, 145 and 1848, **65**, 349.

[3] Barth and Hlasivetz, *ibid.*, 1864, **130**, 354.

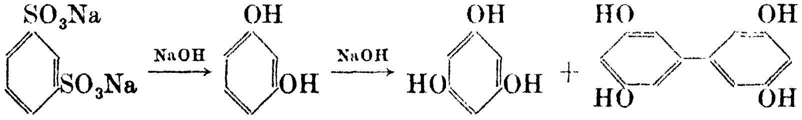
Oxidation of catechol by dry silver oxide in ether yields *o*-benzoquinone[1] (194), whilst catalytic reduction gives *cis*-quinite (*cis*-*cyclo*-hexane diol) (190).



With halogens, it is possible to obtain tetrachloro- or tetrabromo-catechol; excess of the reagent oxidises it to the corresponding tetrahalogen substituted *o*-quinone (191). Thionyl chloride gives a thionyl catechol (192), and thiocarbonyl chloride gives a thiocarbonyl catechol (193).

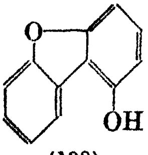
Many of the ethers and half ethers of catechol are of considerable importance (see Phenol Ethers, p. 335).

Resorcinol is obtained by the dry distillation of numerous natural resins and products; one of the best is the impure brazilin, which separates from Brazil wood extracts on standing. The method universally used in industry is the caustic fusion of the sodium salt of benzene-*m*-disulphonic acid (195) readily obtained by the sulphonation of benzene. The time of fusion and amount of alkali must be restricted or the reaction proceeds further with the formation of phloroglucinol (196) and diresorcin (197). It is interesting to note that benzene-*p*-disulphonic acid also gives resorcinol on caustic fusion, as do all three brombenzene sulphonic acids. Resorcinol forms large prismatic crystals, m. 119°, b. 276°; it has a faint odour (somewhat reminiscent of α-naphthylamine) and a pronounced antiseptic action, being used in this capacity in dermatological practice.



(195) (196) (197)

Resorcinol is capable of a wide range of chemical changes, and whilst the bulk of industrial resorcinol is used as an end-component in the dyestuffs industry, it can also be used as a starting point for syntheses. Thus, on pyrolysis over tungstic acid at 500-550° it yields a mixture of hydroxy diphenylene oxide and dihydroxy diphenylene oxide (198) and (199).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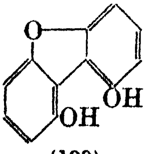
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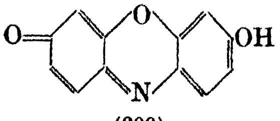
(200)

Resorcinol may be converted almost quantitatively to *m*-phenylene diamine by autoclaving with ammoniacal ammonium sulphite solution, whilst it condenses readily with *p*-amino phenol to give resorufin (200).

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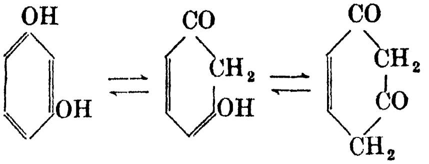
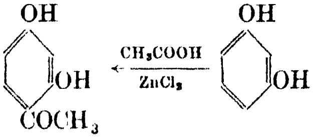
[1] Willstätter, *et al.*, *Ber.*, 1904, **37**, 4744.

Many reactions of resorcinol are best interpreted upon the assumption that it can exist in the mono- and di- ketonic tautomeric forms :—



Thus, resorcinol reacts readily with acetic acid in the presence of zinc chloride to form resacetophenone (201). The reaction is general, and can be



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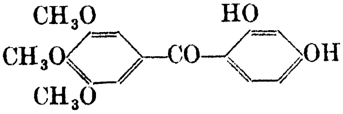
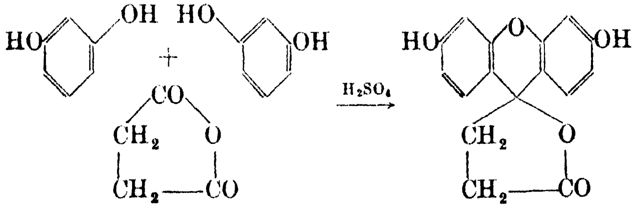


(202)

carried out with most organic acids ; thus trimethylgallic acid yields the 3, 4, 5-trimethoxy-2′, 4′dihydroxybenzophenone (202).

Acid anhydrides, particularly cyclic anhydrides, also react readily with the 'active' hydrogen of resorcinol ; the reaction is of wide application, succinic and glutaric anhydrides from the aliphatic section, and nearly all homologues and analogues of phthalic acid give the reaction. Compounds from succinic, glutaric, phthalic and diphenic anhydrides are shown in formulæ (203) to (207).



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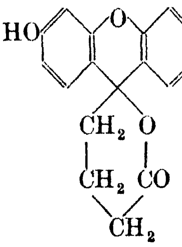

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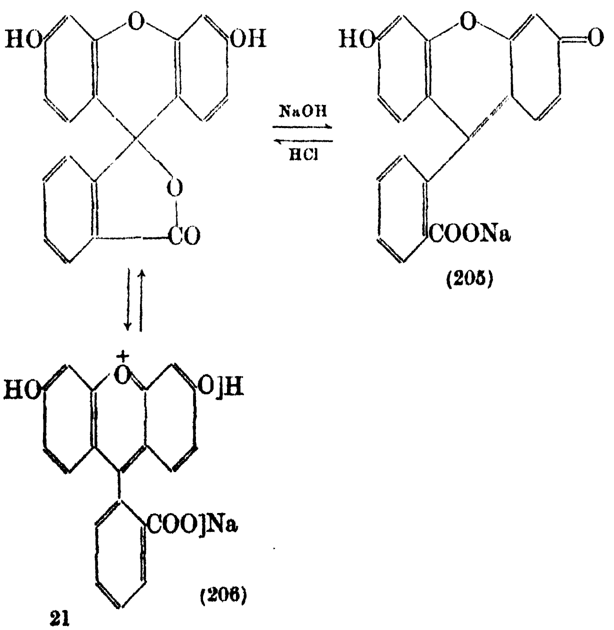

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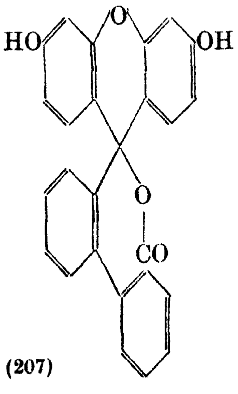
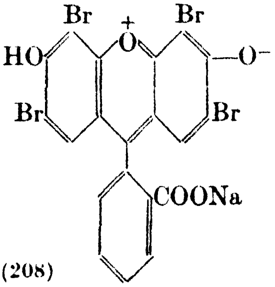


(207)

All the members of this class show fluorescence, and the group are known as 'fluoresceins'. The name 'fluorescein' is usually applied to the compound from resorcinol and phthalic anhydride which, on solution in alkalies, produces so intense a fluorescence that its presence is used as a test both for resorcinol and for phthalic anhydride. The structure of this alkaline fluorescein has usually been conveniently represented by the formula (205) embodying a quinonoid structure analogous to that of the phthaleins. It appears, however, that the two hydroxyl groups are intact, and that an oxonium form is obtained (206) by the action of alkali. The derivatives of fluorescein are brilliantly coloured and although, in the majority of cases of little value as dyestuffs, one or two of them have a limited industrial application. Some typical examples are set out below :—



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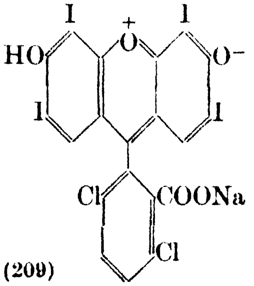

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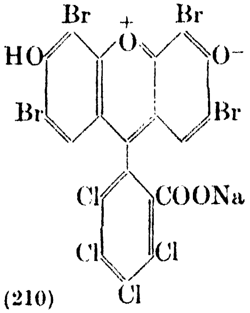

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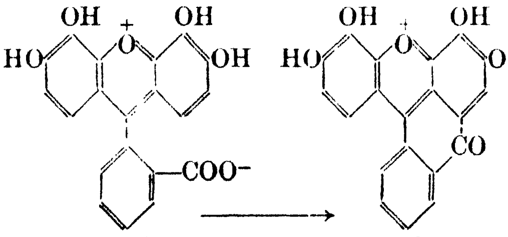


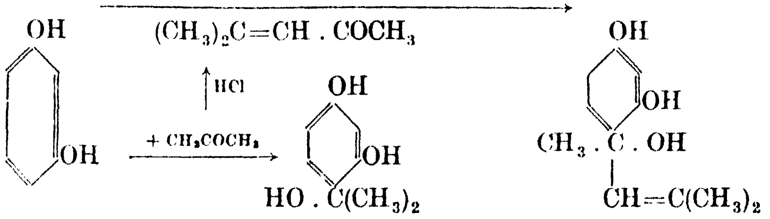
(211) (212)

Tetrabromofluorescein (208) or Eosin, is a brilliant red substance used for many kinds of red ink, in cosmetics, and for dyeing silk. Its ethyl ester forms a sodium salt which is soluble in spirit, and is called 'Spirit Eosin'. The dye Rose Bengal (209) is made by condensing dichlorophthalic anhydride with resorcinol and iodinating the product. Apart from its use as a histological stain, it is used in dyeing silk a brilliant pink.

Phloxine (210) is obtained from tetrachlorophthalic anhydride and resorcinol, followed by bromination. Its main application is as a histological stain.

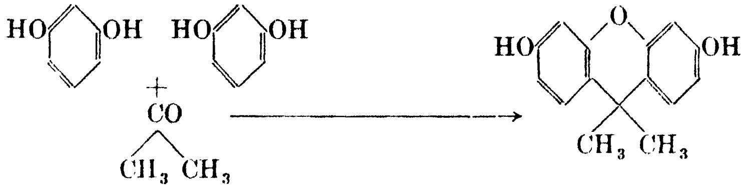
The condensation to fluoresceins proceeds equally well with gallic acid, and the primary substance formed is the gallein (211). The action of sulphuric acid on this substance leads to ring closure through the carboxyl group, giving a substance cœrulein (212), the chromium lake of which is an extremely fast blue silk dye.

Resorcinol will react quite readily with ketones through the labile hydrogen position ; the hydrogen becomes attached to the oxygen of the ketone and a tertiary alcohol is obtained. Thus, with acetone a little dihydroxyphenyl dimethyl carbinol (213) is obtained ; the bulk of the acetone is, however, converted to mesityl oxide by the hydrogen chloride used as a condensing agent, so that the main product is dihydroxyphenyl methyl *iso*-butenyl carbinol (214).



(213) (214)

If zinc chloride is added to the reaction mixture, the condensation with acetone takes another course, forming xanthenes (215).

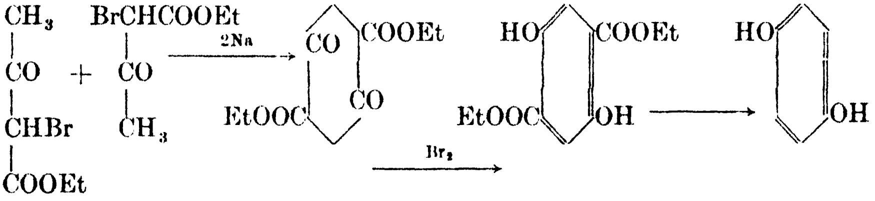


(215)

HYDROQUINONE

Wöhler used a variety of reducing agents to prepare hydroquinone from quinone; they included hydriodic acid and hydrogen telluride—but he concluded that sulphur dioxide is the most suitable reagent for the purpose. Industrially, iron and sulphuric acid is used.

This method has served for the production of hydroquinone ever since; it is a substance manufactured in considerable quantity for photographic purposes, being a good developer (i.e. it reduces silver salts in the cold). It has been synthesised by alternative routes involving the condensation of two molecular proportions of bromoacetoacetic ester using sodium. The reaction is then continued as follows:—

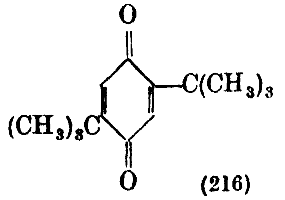


It is also interesting to note that hydroquinone can be obtained by the action of hydrogen peroxide on phenol, and also in very small quantity during the fusion of phenol with alkalies. In addition, small quantities of hydroquinone are found in the products of pyrogenic decomposition of many aliphatic compounds, especially the salts of succinic acid.

Hydroquinone forms well-defined leaves or prisms (usually the latter) which melt at 169°; it is fairly soluble in water, and distils and sublimes unchanged.

The oxidation of hydroquinone has been the subject of much study, partly on account of the ease with which it passes into quinhydrone and quinone, and partly on account of the widespread use of hydroquinone as a developer. The oxidation of aqueous solutions of hydroquinone by aerial oxygen is catalysed by traces of manganese. The reputed catalytic action of certain of the enzymes of lucerne and of lac is due to their content of manganese, which may, of course, be the cause of their activity in other directions.

Whilst in the majority of reactions hydroquinone behaves as a phenol, forming ethers normally, it has one or two reactions which are unusual. Thus, when shaken with a solution of ferric chloride and *ter*-butyl alcohol, it gives a di-*ter*-butyl quinone (216).

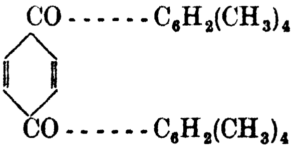


(216)

Wöhler, in 1884, described a 'green hydroquinone' which he obtained by the cautious reduction of quinone, or the correspondingly cautious oxidation of hydroquinone. Later he found that by mere admixture of quinone and hydroquinone solutions the 'green hydroquinone' was instantly formed. Wöhler became lyrical about his new compound :—

> "Green hydroquinone is one of the most beautiful substances which organic chemistry has produced. It is very similar to murexide, but excels it in lustre and beauty of colour. In this respect it bears the greatest resemblance to the metallic green of the rose-chafer, or of the feathers of the humming bird. . . ."

This compound is only one of a long series which depend for their existence on the fact that the subsidiary valency of the oxygen in *p*-quinone is not fully occupied, presumably due to a weakening of this bond by the benzoquinonoid ring. Thus, all simple phenols, amines and some hydrocarbons form 'quinhydrones'. Durene forms a blood-red double compound (217), and the



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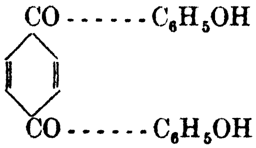

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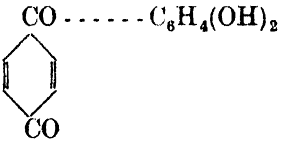
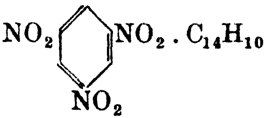


(219)

phenol compound is analogous (phenoquinone, No. 218). The most satisfactory way of regarding such compounds is as if the residual affinity of the oxygen of the keto or quinone group is satisfied by a field of affinity set up by the whole of the adduct, by virtue of its benzenoid character. The whole field of molecular compounds has been the subject of much research, the results of which were summarised by Pfeiffer in 1927 (see Appendix I). The constitution of quinhydrone is usually written as in (219), only one quinonoid group being involved ; there is, of course, the possibility that the second group is to some extent involved, but it must be remembered that it is the *whole* residual affinity of the aromatic structure which satisfies the residual oxygen affinity. These phenomena are entirely in line with the formation of hydrocarbon picrates, styphnates, and the molecular compounds of trinitrobenzene and its analogues, where a precisely similar relation exists between the nitro group and the general residual affinity of the aromatic structure, as in (220), the compound between trinitrobenzene and anthracene. The halochrome salts obtained with acids and γ-pyrone structures are also best interpreted as examples of the same tendency (221). Hydroquinone is also able to exercise a salt-forming action with amines ; it forms stable, crystalline products with ethylamine, benzylamine, dimethylamine, diethylamine and many others. The condensation of hydroquinone with acetoacetic ester in the presence of sulphuric acid to give a methylhydroxycoumarin (222) is an important synthetic method.



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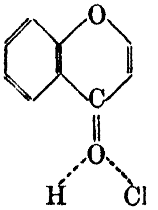

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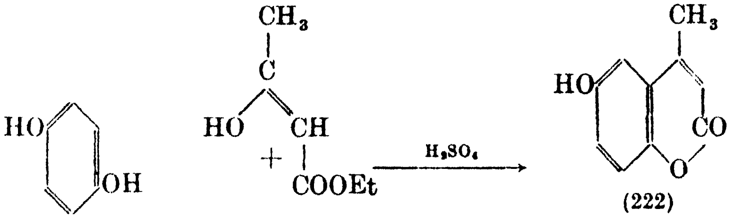


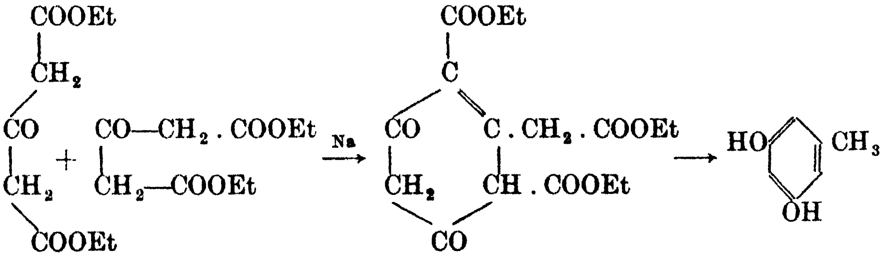
(222)

ORCINOL

Comment has already been made on the first isolation of orcinol and its related compounds from lichens. It may be obtained from suitable lichens by boiling with lime-suspension in water, filtering, and precipitating the tannins and pigments with dilute hydrochloric acid. The filtrate is limed again and the orcinol extracted with benzene after removal of the calcium and evaporation.

Orcinol is obtainable by the caustic fusion of a large variety of *m*-substituted compounds, such as symmetrical bromotoluenesulphonic acid, *s*-dibromotoluene, etc.

From aliphatic sources it can be obtained from the following sequence of reactions. Acetone dicarboxylic ester (223) is condensed with itself in the presence of sodium to give a homologue of diketocyclohexenetricarboxylic ester (224). This, on saponification, gives an orcinol carboxylic acid, which, in turn, can, after hydrolysis, be converted to orcinol by loss of CO_2.



(223) (224)

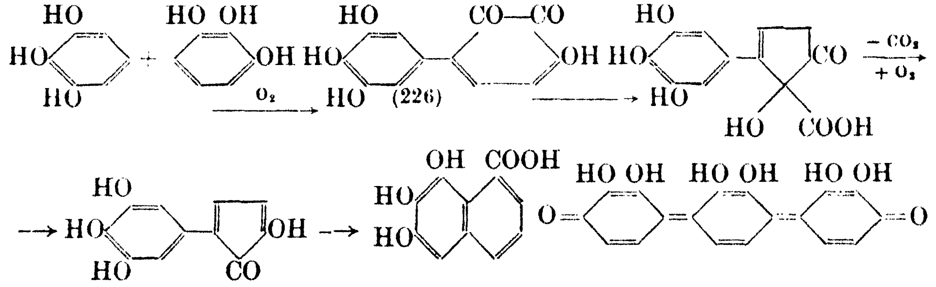
Orcinol forms large crystals, m. 107-108°, when anhydrous. In general, its chemical reactions are analogous to those of resorcinol; contrary to the statement of Whitmore, it forms an orcinol-phthalein, homologous with fluorescein. If orcinol is warmed with a little chloroform and caustic potash, a purple-red colour is produced and on diluting the solution, an intense greenish-yellow fluorescence is observed. When fused with alkali, orcinol is converted to phloroglucinol.

TRIHYDROXYBENZENES

Scheele, in 1786, obtained pure gallic acid, and by the action of heat obtained pyrogallic acid, or pyrogallol. It is not clear whether or not he regarded it as an entirely new product; but he was surprised to find that gallic acid and the sublimed material both gave a precipitate with ferrous sulphate. For many years it was regarded as a purified gallic acid until Gmelin distinguished it from the former acid. Berzelius, in 1845, established its composition. The method of Scheele is still the only method of obtaining this compound which is practicable; it has been slightly modified, and the decarboxylation is now carried out by heating gallic acid with half its weight of water in an autoclave at 200-210°.

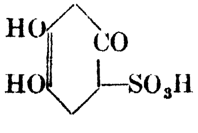
Pyrogallol (1, 2, 3-trihydroxybenzene) forms needles, m. 132°; b. 309°.

Pyrogallol is associated in the mind of practical chemists mainly with its use as a photographic developer, and its use in gas analysis for the absorption and estimation of oxygen; alkaline solutions of pyrogallol rapidly absorb oxygen becoming a deep brown colour. The main substance produced in this absorption is purpurogallin (225), which was obtained in good yield by Willstätter and Heiss [1] by oxidising pyrogallol with ferricyanide. Purpurogallin is a substance which appears to have the cyclopentadienone structure (225), and is presumed to be formed by the sequence of reactions shown above. The o-quinonoid diphenyl derivative (226) is unstable, and passes by an extrusion reaction to trihydroxy-2-phenyl-5-hydroxy*cyclo*-pentadienone (225), or purpurogallin. Acids convert the latter substance to a trihydroxy naphthalene carboxylic acid (227), which was characterised by Perkin.[2] This sequence of reactions by no means exhausts the changes taking place during the absorption of oxygen by alkaline pyrogallol; there is, in addition, always a little carbon monoxide produced, and several other organic substances are formed, including 2, 3, 2′, 3′, 2″, 3″-hexahydroxytribenzoquinone (228).



(225) (227) (228)

Pyrogallol is very reactive, and shows an unusual lability of structure, which is probably due to its ability to assume a partly ketonic form; it reacts with bisulphite to yield 3-keto-5, 6-dihydroxy-1, 2, 3, 4-tetrahydro benzene-2-sulphonic acid (229) in which, by some deep-seated change, the oxygen of the third hydroxyl group has migrated. Aldehydes and ketones react readily with pyrogallol, either through the ring as in the case of the dyestuff base (230) obtained



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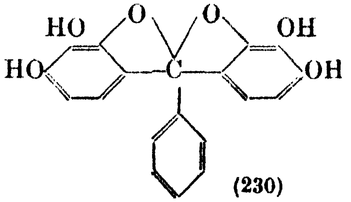

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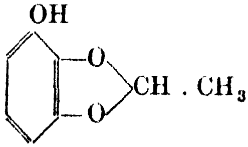

(231)

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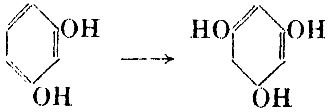
[1] Willstätter and Heiss, *Ann.*, 1923, **433**, 17-33.

[2] Perkin and Stevens, *J.C.S.*, 1903, **83**, 193.

from pyrogallol and benzaldehyde in the presence of hydrochloric acid at 100°, or through the hydrogen atoms of two adjacent hydroxyl groups, as in the case of the reaction with acetaldehyde (231).

Phloroglucinol, 1, 3, 5-trihydroxybenzene is the only other trihydric phenol commonly met with. It occurs naturally as part of several glycosides, particularly phloridzin, which is found in the root bark of the apple and pear. The chemistry of phloridzin is discussed in connexion with the subject of glycosides (Chap. VIII), and it was from phloretin (the aglycone of phloridzin) that Hlasiwetz,[1] in 1855, first prepared phloroglucinol; he coined the name to indicate the origin of the material and its sweet taste.

Phloroglucinol (232) is manufactured by two methods; in the U.S.A. by the caustic fusion of resorcinol :—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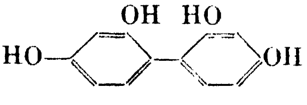
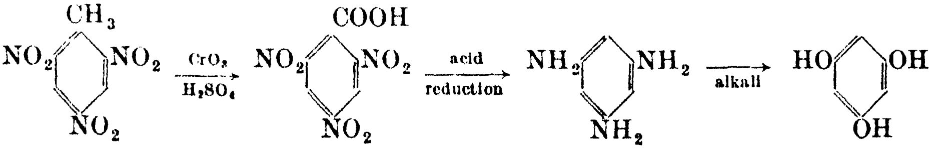

(233)

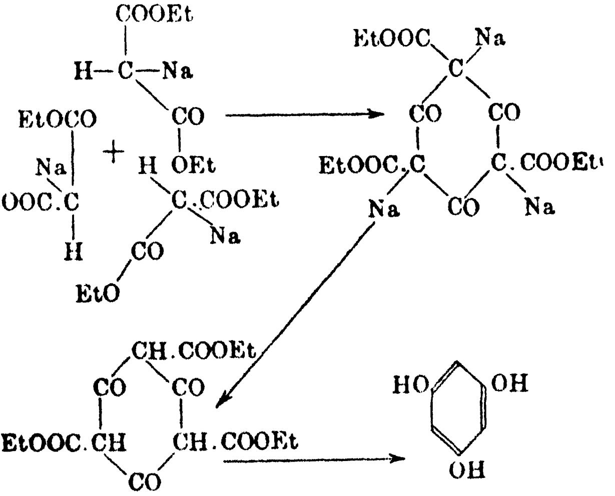
The process has the drawback that di-resorcin (233) is produced at the same time, and it is difficult completely to separate it from the phloroglucinol. The presence of di-resorcin in phloroglucinol is a serious disadvantage in the production of dye-line prints.

In England, phloroglucinol is manufactured by oxidation of trinitrotoluene to trinitrobenzoic acid (234), followed by acid reduction in which reduction of the nitro groups and decarboxylation to triaminobenzene (235) takes place. The liquor is then boiled with alkali and the three amino groups of the triaminobenzene are hydrolysed to hydroxyl (236). By this process a pure product is obtained.



(234) (235) (236)

Phloroglucinol can also be obtained by heating sodiomalonic ester to 145°, when the following reaction takes place :—



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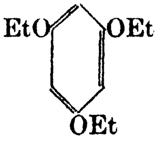
[1] Hlasiwetz, *Ann.*, 1855, **96**, 118.

On treating the residue with dilute hydrochloric acid and boiling, the ester groups are hydrolysed, carbon dioxide is lost, and phloroglucinol formed.

The industrial value of phloroglucinol lies in its ability to couple with three molecules of a diazo compound to produce a deep purple, almost black dye. This is the basis of the so-called dye-line prints used by architects and engineers in the copying of plans and drawings. Paper impregnated with a stabilised diazo compound is covered by the semi-transparent tracing of the drawing to be reproduced and the whole is submitted to ultra-violet light from a mercury arc. The diazo-compound in the portions exposed is destroyed; that in those places covered by the dark lines of the drawing is preserved. The paper is then passed between rollers moistened with a buffered solution of phloroglucinol when coupling takes place between three molecules of diazo-compound and one of phloroglucinol, thus giving a dark line wherever a similar dark line exists in the original tracing.

The structure of phloroglucinol shows a definite tautomerism between the trihydroxyphenol and the triketo form. Thus, all the common reactions of a phenol are given, such, for example, as the formation of ethers e.g. triethyl phloroglucinol (237), and the coupling with diazonium compounds; on the other hand, phloroglucinol forms a trioxime (238), a crystalline substance exploding at 155°. A solution of phloroglucinol decolorises iodine, but although the iodine cannot be extracted by carbon disulphide, evaporation of the solution leaves only phloroglucinol behind, the iodine passing off with the vapour during evaporation. When phloroglucinol is treated with concentrated ammonia, phloramine (239) is obtained. With amines, the reaction is more deep-seated; with ethylamine, a diethylamino compound is formed (240) and with aniline, three molecules react to give the compound (241). There is no doubt that the keto-form assists in the formation of these compounds. Phloroglucinol forms addition compounds with one, two or three molecules of sodium bisulphite.



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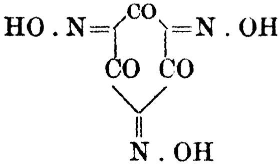

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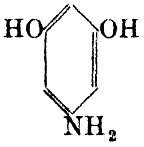

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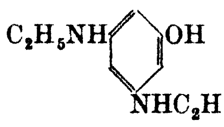

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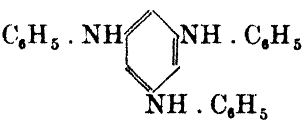
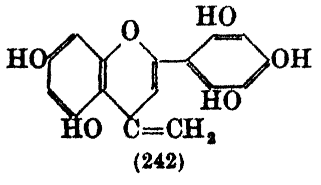


(241)

Phloroglucinol reacts with glacial acetic acid, first to give an acetyl derivative, but in the presence of zinc chloride the reaction proceeds further and the pyrone derivative (242) is obtained. Phloroglucinol also combines readily with nitriles.



(242)

The third trihydric phenol, 1, 2, 4-trihydroxybenzene, or hydroxyhydroquinone is a substance but little known. It is obtained by the caustic fusion of hydroquinone, during which operation an additional hydroxyl group enters the ring. It is extracted by ether from the acidified melt and may be crystallised from warm water; it forms monoclinic crystals, m. 141°.

Several higher hydroxybenzene derivatives are known, of which the m. pts. are given below:—

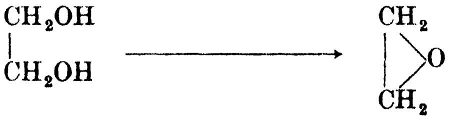
1, 2, 3, 4-Tetrahydroxybenzene, m.p. 79°, Apionol.
1, 2, 3, 5-Tetrahydroxybenzene, m.p. 165°, Hydroxyphloroglucinol.
1, 2, 4, 5-Tetrahydroxybenzene, m.p. 215°.

THE ETHERS

Ethers may be regarded as anhydrides derived by the elimination of the elements of one molecule of water from two of alcohol:—

$$R.OH + HO.R \longrightarrow R.O.R$$

This reaction takes place quite readily, and in the case of substances in which two hydroxyl groups are attached to the same carbon chain, a cyclic ether is obtained.



Such a configuration is often referred to as an oxide (e.g. ethylene oxide), and the internal ether group is named an "epoxy" group.

The history of our knowledge of ether goes back to the sixteenth century when a German physician, Valerius Cordus, obtained ether by mixing thrice rectified spirit of wine with oil of vitriol, and after allowing the mixture to stand for some time, distilled off the ether on the water bath. Many of the older chemists mention a similar spirit, and Basil Valentine refers to a substance of "subtle, penetrating, pleasant taste, and agreeable smell". Little was heard of the properties of this substance until in 1730 Frobenius published a paper [1] on the "*spiritus vini æthereus*" in which he described many of the properties of ether, but did not give the method of its preparation, which was kept secret until after his death in 1741. When his method of preparation was finally published it was found to be merely a modification of the older process whereby spirit of wine was dehydrated by sulphuric acid; he had, however, observed that a moderate amount of acid would serve for the dehydration of a considerable amount of alcohol, the same acid being used over and over again, the ether and water distilling together, leaving the acid almost unimpaired in its dehydrating properties. This explanation of the action of sulphuric acid was not mentioned by Frobenius, but was first propounded by Fourcroy in his treatise on chemistry at the commencement of the nineteenth century. The continual use of sulphuric acid for many successive quantities of alcohol was a puzzle for the chemists of that time, and they were at a loss to account for the fact that the acid, after having extracted the water from the alcohol, parted with it so readily. The mystery deepened with the introduction by Boullay [2] of a "continuous" ether process, and in the absence of a proper explanation the "theory" of catalytic action was devised by Mitscherlich [3] (Roscoe, on this procedure quoted the comment:—

"Denn eben wo Begriffe fehlen
Da stellt ein Wort zur rechten Zeit sich ein").

---

[1] Frobenius, *Phil. Trans.*, 1729-30, **36**, 283.
[2] Boullay, *Dissertation sur l'éther*, Paris, 1815.
[3] Mitscherlich, *Pogg. Ann.*, 1834, **31**, 273.

Gradually, however, the following facts came to light :—

1. The first product of the action of sulphuric acid on alcohol is ethyl sulphuric acid.
2. Ethyl sulphuric acid, when heated with water was observed to give ether ; an observation which led Liebig to the belief that the ether was formed by the decomposition of ethyl sulphuric acid into ether, sulphuric acid and sulphur trioxide, which, of course, combined with the water present to regenerate sulphuric acid.
3. Graham noted that when pure ethyl sulphuric acid is heated alone, no ether is produced, thus invalidating the previous workers' conclusions.
4. Williamson, in 1850, by using a fresh conception of the structure of ether, was able to advance what is substantially the correct explanation of its formation.

Williamson, adopting the Laurent-Gerhardt conception of the formula of ether as $C_4H_{10}O$, propounded the view that just as alcohol could be considered as water in which one atom of hydrogen had been replaced by the ethyl radicle, so ether could be considered as the product obtained by the replacement of both hydrogen atoms by ethyl radicles. He made many experiments to attempt to substantiate his view ; he was the first to react " ethylate of soda " with " iodide of ethyl " to obtain ether :—

$$C_2H_5O\,.\,Na + I\,.\,C_2H_5 \longrightarrow C_2H_5OC_2H_5 + NaI$$

whilst his explanation of the continuous formation of ether was epitomised in the two equations :—

$$1.\ C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5\,.\,SO_4H + H_2O$$
$$2.\ C_2H_5OH + C_2H_5SO_4H \longrightarrow C_2H_5OC_2H_5 + H_2SO_4,$$

and by carrying out the second reaction with pure substances, he was able, experimentally, to verify his hypothesis.[1]

The validity of the second equation was soon proved, both by Williamson and others, by the preparation of mixed ethers from ethylsulphuric acid and other alcohols.

The catalytic theory has by this time been almost lost sight of ; Senderens pointed out, however, that the amount of sulphuric acid required for etherification of an alcohol decreased very considerably as the molecular weight of the alcohol increased, until with the higher alcohols only 1 or 2 per cent. of acid was required. His results are summarised in Table VII.

TABLE VII

QUANTITIES OF SULPHURIC ACID REQUIRED FOR ETHERIFICATION

Alcohol	Temperatures			Sulphuric Acid (vol. per cent. of alcohol).
	B.P. Alcohol	B.P. ether	Temp. for etherification	
Ethyl	78°	35°	125-130°	100
Propyl	97°	88°	120-125°	40
Butyl	117°	141°	123-126°	25
***iso*-Butyl**	108°	123°	120-122°	20
***iso*-Amyl**	130°	171-172°	130-135°	10
Heptyl	175°	262°	140-145°	3
Cetyl	344°		140-145°	2
***iso*-Propyl**	83°	68°	98-100°	15
***sec*-Butyl**	101°	120°	103-104°	5
Pentanol-2	118°	162°	120°	2·5
Octanol-2	179°	263°	135°	1·5

---

[1] Williamson, *Phil. Mag.*, 1850, **337**, 350.

This data, and subsequent evidence that in some cases even smaller quantities of acid could bring about etherification, led to a recognition of the dual role of sulphuric acid in the process ; as a dehydrating agent, when present in quantity, and as a catalyst in cases where the equilibrium

$$R . OH + HO . R \rightleftarrows R . O . R + H_2O$$

lies sufficiently on the right-hand side to render dehydration unnecessary.

The main drawback to the use of sulphuric acid in ether formation, is not that it is ineffective, but that it induces dehydration in other directions leading to the formation of hydrocarbons, and even of carbon itself, and that it is, itself, partly reduced with the formation of sulphur dioxide. This may be avoided by the use of dilute acid in many cases, and Senderens was successful in applying acid of the composition $H_2SO_4, 3H_2O$ to the formation of ethers in cases where the strong acid was either unsuccessful or led to side-reactions. Two cases in point are the etherification of benzyl alcohol, and allyl alcohol, the latter exploding in the presence of a small quantity of strong sulphuric acid, whilst with dilute acid the ether is formed normally. The use of sulphuric acid of this strength is particularly valuable in the formation of aralkyl ethers, and by its use benzyl, cinnamyl, phenylethyl and *cyclo*hexylbenzyl alcohols are readily converted to the corresponding ethers.

There are several other methods by which the force of the strong acid may be mitigated; thus, both alkali hydrogen sulphates and sulphonic acids can be used as reagents for etherification. With the bisulphate, the action appears to take a course parallel with that observed when sulphuric acid alone is used ; with benzene sulphonic acid, however, a definite intermediate stage is easily isolated :—

$$C_6H_5SO_3H + HO . R \longrightarrow C_6H_5SO_3R + H_2O$$
$$C_6H_5SO_3R + HO . R \longrightarrow R . O . R + C_6H_5SO_3H$$

The isolation of the intermediate sulphonic ester enables mixed ethers to be prepared :—

$$R'OH + C_6H_5SO_3R'' \longrightarrow R' . O . R'' + C_6H_5SO_3H$$

There are several reactions by which ethers may be prepared, which obviate the use of a dehydrating acid ; a number of these are indicated below :—

1. The use of dimethyl or diethyl sulphates for the conversion of hydroxyl compounds to their methyl or ethyl ethers. Thus, phenols of all descriptions are converted to the corresponding ethers when treated in alkaline solution with dialkyl sulphates. This reaction is equally applicable to aliphatic compounds, and has proved of paramount value in the investigation of glycosides. In the case of phenols the yields are exceptionally good.
2. In cases where other methods fail, the original method of Würtz can often be used. This involves treatment of the corresponding alkyl iodide with silver oxide :—

$$(CH_3)_3C . I + Ag_2O + I . C(CH_3)_3 \rightarrow (CH_3)_3C . O . C(CH_3)_3$$

The reaction has the advantage of proceeding at a low temperature, so that isomeric changes can, to a large extent, be avoided.

3. The method of Williamson, indicated previously in this chapter, can be used successfully for the preparation of mixed ethers.
4. An ingenious method of obtaining aralkyl ethers was devised by Sigmund and Marchand,[1] in which an acetal is submitted to catalytic reduction by hydrogen in the presence of nickel :—

$$C_6H_5 . CH_2 . CH(OEt)_2 + H_2 \longrightarrow C_6H_5 . CH_2 . CH_2 . OEt + C_2H_5OH$$

When the acetal of phenylacetaldehyde is reduced in this way, β-phenylethyl ethyl ether is obtained, which is a valuable perfumery substance.

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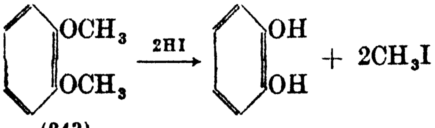
[1] Sigmund and Marchand, *Monatsh.*, 1927, **44**, 267, 288.

The ethers are largely valued for their solvent and physiological properties, being comparatively inert chemically; indeed, it is difficult to associate any functional reactions with the ether group. The following reactions are those most generally given by ethers, and are mainly decompositions.

1. The action of hydriodic acid on simple ethers is to regenerate the hydroxyl group, leaving the second radicle in the form of an iodo compound. Thus, with veratrole (243), two molecules of methyl iodide are formed,



(243)

and catechol is regenerated. In the case of simple ethers a similar reaction is observed :—

$$C_2H_5 . O . C_2H_5 + HI \longrightarrow C_2H_5OH + C_2H_5I$$

Naturally, if the concentration of the acid is sufficiently high and the conditions of reaction are appropriate, the second molecule of alcohol will yield ethyl iodide as well. In cases where the conditions are such that the second molecule is not converted to the iodide, the iodine appears invariably to become attached to the smaller residue;

thus, $CH_3(CH_2)_5OCH_3 + HI \longrightarrow CH_3(CH_2)_5OH + CH_3I$

when methyl hexyl ether is treated with hydriodic acid, methyl iodide is almost exclusively produced. This reaction forms the basis of Zeisel's method for the determination of methoxy and ethoxy groups in aromatic substances, whereby the methyl and ethyl iodide produced from such groups is volatilised out of the reaction mixture in a current of carbon dioxide and decomposed by passage through alcoholic silver nitrate solution; the silver iodide produced is a measure of the original alkoxy groups.

2. With many ethers it is possible to detect the addition of halogen acids to the ether oxygen, which behaves as though it is only partially saturated; a similar addition is observed with the Grignard reagent, and accounts for the obstinate retention of ether by compounds such as magnesium ethyl iodide. This subject is discussed more fully in Vol. II.

3. Acyl and phosphorus halides attack ethers; the action of acetyl chloride in the presence of zinc chloride upon a typical ether is shown in the two equations :—

$$CH_3(CH_2)_5OCH_3 + CH_3COCl \longrightarrow CH_3(CH_2)_5Cl + CH_3COCH_3$$
$$CH_3(CH_2)_5OCH_3 + CH_3COCl \longrightarrow CH_3Cl + CH_3(CH_2)_5COCH_3$$

The mixture of chlorides and ketones is difficult to separate.

4. Ethers can be chlorinated, but the compounds formed are usually mixtures of the mono-, di- and tri- chloro compounds, together with the compounds obtained by the action of the hydrogen chloride formed, on the ethers, and only in rare cases can a satisfactory yield of the monochloro ether be obtained.

Some Individual Ethers

Dimethyl ether, CH_3OCH_3, was discovered by Dumas and Peligot in 1835 by the action of sulphuric acid on methanol; they called it "methylene hydrate". The substance is best prepared by this method, and is a gas boiling at − 21°. It is readily absorbed by sulphuric acid, which takes up 600 times its volume and the ether can be released by allowing the acid solution to drop into an equal volume of water. At one time dimethyl ether was used as a refrigerant, but has been displaced by substances which are more satisfactory from a thermodynamic standpoint, and which are less inflammable. Dimethyl ether is moderately soluble in water, which at 15° dissolves about 40 volumes of the gas. If, at some future time, it becomes necessary to use large quantities of dimethyl ether it could readily be obtained by passing the vapour of methanol over a mass of alumina at 250°. The conversion to the ether is almost complete.

Chemically, the most interesting reactions of dimethyl ether are those with the halogens. Straight admixture of the ether and chlorine at ordinary temperatures leads to explosion ; but by suitably diluting the reactants chloro derivatives of dimethyl ether can be obtained.

The monochloro derivative $ClCH_2OCH_3$, is best prepared by the action of a stream of hydrogen chloride on a mixture of methanol and formaldehyde ; it is a liquid of somewhat lachrymatory tendency, b. 59°. The following chloro- and bromo- derivatives of dimethyl ether are also known :—

1. *s-Dichlorodimethyl ether* $ClCH_2OCH_2Cl$.—This is the lowest chlorinated compound obtainable in quantity by the direct chlorination of dimethyl ether. It is a colourless liquid with a penetrating smell, b. 105°, and is very soable. With water it is converted to hydrochloric acid and trioxymethylene, and may be obtained from the latter by the action of phosphorus trichloride.
2. *Trichlorodimethyl ether*, b. 131°.
3. *Tetrachlorodimethyl ether*, b. 130°.
4. *Hexachlorodimethyl ether*, which, with the two previous compounds, is obtained during the direct chlorination of the ether. It is unstable, and decomposes at about 100° to give carbon tetrachloride and phosgene

$$Cl_3C\,.\,O\,.\,CCl_3 \longrightarrow CCl_4 + COCl_2$$

5. The following derivatives from the higher halogens are also known :—

Monobromodimethyl ether, b. 87°
Monoiododimethyl ether, b. 124°
s-Dibromodimethyl ether, b. 155°
s-Di-iododimethyl ether, b. 211°

Diethyl ether, $C_2H_5O\,.\,C_2H_5$, may be obtained by any of the general methods outlined above ; in industrial practice, the production of ether is carried out either by passage of alcohol vapour through heated glacial phosphoric acid, or by the passage of preheated alcohol vapour over a contact mass of alumina at temperatures round about 250-280°.

Diethyl ether is a limpid colourless liquid, b. 34·6°, and remaining liquid down to − 125°. It is an excellent solvent, and finds considerable application in this capacity both in the laboratory and in industrial plant. The major disadvantage in the use of ether as a solvent for extraction from aqueous solutions lies in its solubility in water. Thus, at 12°, water dissolves one-tenth of its volume of ether, and ether one-fiftieth of its volume of water. The effect of this is that considerable amounts of ether remain in the extracted liquid, and the ethereal extract contains about 2 per cent. of water, which will, of course, remain behind when the ether is removed by distillation. Many substances, both organic and inorganic, such as ethanol or hydrogen chloride, increase the solubility of ether in water. The replacement of ether by methylene dichloride as a solvent for extraction obviates these disadvantages, as well as removing the fire hazard.

The chemical properties of ether are typical of the group ; oxidation in air is readily brought about, and in excess of ether vapour considerable amounts of acetylene are produced ; ether vapour in moist air gives some hydrogen peroxide, whilst in the presence of a heated platinum surface, ether is oxidised to trioxymethylene peroxide. Such peroxide compounds sometimes accumulates in the " still-bottoms " of stills used to recover ether, and have caused dangerous explosions. One of the best methods for preventing such explosions is to add a little alcohol to " used " ether before recovery ; the alcohol decomposes the peroxides quietly and is not itself carried over through the column into the distillate.

Apart from its solvent activity, ether is valued as an anæsthetic ; this property appears first to have been applied, but imperfectly published, by Dr. C. W. Long in America, and although he carried out surgical procedures with ether anæsthesia in the period 1842-1845, his failure to effect publication led to confusion of his claim for priority with those of Morton and Jackson, who about this time had observed the anæsthetic action of ether. In this country the use of ether was introduced and popularised by Sir James Simpson of Edinburgh, who persevered with its use in surgery, despite considerable opposition. The ether used for anæsthesia must be free from traces of aldehydes and peroxides, and is usually stored in completely full bottles of non-actinic glass, out of direct light, and with the addition of a small amount of alcohol which diminishes the aldehyde formation and combines with any traces of aldehyde that may be formed. Many symmetrical and unsymmetrical ethers have been prepared ; some of the more important are listed in Table VIII.

TABLE VIII

SOME MEMBERS OF THE ETHER GROUP

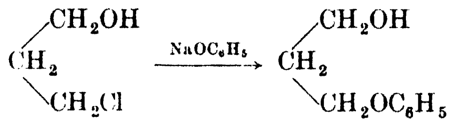
Formula $R_1O . R_2$		B.P.	DENSITY	
Group R_1	Group R_2		$t°$	Density
Methyl	Methyl	—23·5°	—25°	0·7374
Methyl	Ethyl	11°	0°	0·7252
Methyl	Propyl	39°	0°	0·7471
Methyl	Allyl	43°	11°	0·770
Methyl	Propargyl	61°	12·5°	0·830
Methyl	Butyl	71°	13°	0·748
Methyl	*iso*-Butyl	60°	0°	0·7507
Methyl	Amyl	100°		
Methyl	Heptyl	150°	0°	0·795
Methyl	Octyl	173°	0°	0·801
Ethyl	Ethyl	34·6°	0°	0·736
Ethyl	Vinyl	35·5°	0°	0·7625
Ethyl	Propyl	63°	0°	0·7545
Ethyl	*iso*-Propyl	54°	0°	0·7477
Ethyl	Allyl	68°	11°	0·770
Ethyl	Propargyl	82°	15°	0·832
Ethyl	Amyl	120°		
Ethyl	Hexyl	136°		
Ethyl	Heptyl	167°	0°	0·795
Ethyl	Octyl	189°	0°	0·801
Ethyl	Cetyl	m. 20°		
Vinyl	Vinyl	39°		
Propyl	Propyl	89°	14·5°	0·7526
Allyl	Allyl	94°	8°	0·805
Butyl	Butyl	142°	15°	0·7725
Amyl	Amyl	187·5°	0°	0·7988
Heptyl	Heptyl	127°/8 mm.	20°	0·8056
Octyl	Octyl	292°	10°	0·820
Cetyl	Cetyl	m. 55° b. 300°		

There are also a few aralkyl ethers of interest; Cannizzaro, in 1855, prepared dibenzyl ether, $C_6H_5CH_2 . O . CH_2C_6H_5$, by heating benzyl alcohol with anhydrous boric acid in a sealed tube at 120-125°. In 1908 Meisenheimer showed that when benzyl alcohol is heated to 210° with a small quantity of dilute sulphuric acid for two hours, a good yield of dibenzyl ether is obtained. The use of benzenesulphonic acid, or of potassium acid sulphate, also leads to good yields of this ether, which is an oil b. 296-297°. Various mixed ethers of the benzyl series have been prepared, as also has di-*cyclo*hexyl ether; the latter is obtained as a liquid b. 239-240° by a Sabatier reduction of diphenyl oxide.

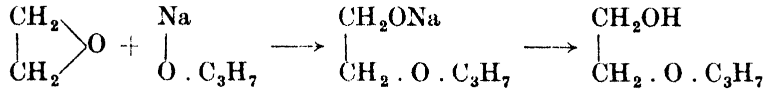
ETHERS OF THE GLYCOL SERIES

The ethers of this series are divisible into three main classes; the simple ethers in which one or both of the hydroxyl groups of the glycol have become etherified; the epoxides or simple ring ethers, and the cyclic ethers such as trioxymethylene. Dealing with the simple ethers first, there is little fresh that can be added to what has already been stated concerning the preparation of ordinary ethers. They are almost universally prepared by heating the monohalohydrins with the sodium derivatives of alcohols or phenols :—

$$HO . CH_2 . CH_2Cl \xrightarrow{NaOEt} HO . CH_2 . CH_2OEt$$

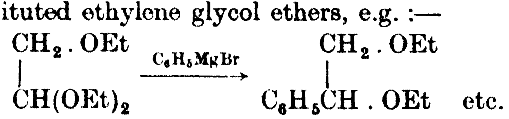


The fully etherified compounds are obtained by a similar procedure applied to the disodium derivatives. With simple glycols, the methyl or ethyl ethers can be obtained by treatment with dimethyl or diethyl sulphate in alkaline medium. An additional method for the preparation of the monoalkyl ethers of ethylene glycol, is the interaction of the sodium derivative of the alcohol with ethylene oxide :—



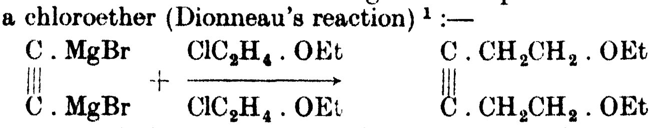
This reaction proceeds readily, and makes the simple half-ethers of ethylene glycol easily available industrially.

Several types of Grignard reagent can be utilised for the preparation of the di-ethers of glycols; thus, alkoxyacetals react with aryl magnesium halides to give aryl substituted ethylene glycol ethers, e.g. :—



$$\begin{array}{l} CH_2 . OEt \\ | \\ CH(OEt)_2 \end{array} \xrightarrow{C_6H_5MgBr} \begin{array}{l} CH_2 . OEt \\ | \\ C_6H_5CH . OEt \end{array} \quad \text{etc.}$$

A somewhat similar method which gives excellent yields of the acetylenic glycol ethers is the interaction of the double Grignard compound from dibromo acetylene with a chloroether (Dionneau's reaction)[1] :—



$$\begin{array}{l} C . MgBr \\ ||| \\ C . MgBr \end{array} + \begin{array}{l} ClC_2H_4 . OEt \\ \\ ClC_2H_4 . OEt \end{array} \longrightarrow \begin{array}{l} C . CH_2CH_2 . OEt \\ ||| \\ C . CH_2CH_2 . OEt \end{array}$$

whilst the unsymmetrical glycol ethers can often be obtained by a variation of Hamonet's reaction[2]

$$EtO . (CH_2)_5 . CH_2MgI + ICH_2 . OMe \longrightarrow EtO . (CH_2)_7OMe$$

The ethers of this series are excellent solvents for the resins and lacquers and are widely used industrially in this capacity.

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[1] Dionneau, *C.R.*, 1906, **142**, 92; 1907, **145**, 128.

[2] Hamonet, *Bull. Soc. Chim.*, 1905, **333**, 528.

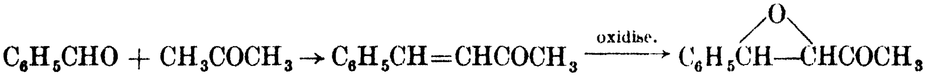
THE EPOXIDES

Wurtz, in 1859, discovered the first epoxide, ethylene oxide, by the action of potash on glycol chlorhydrin, and recognised its nature. Very few epoxides occur naturally, cineole and chenopodiole being exceptions, as also is the 2, 3-epoxybutane found by Henry and Paget [1] in chenopodium oil. The nomenclature of this series of compounds has been derived from two main systems, one of which uses the term " oxide " and relates the compounds to the appropriate unsaturated hydrocarbon, e.g. " ethylene oxide ", while the second system uses the prefix " epoxy " in conjunction with the name of the saturated hydrocarbon, e.g. " epoxyethane ". Whilst the " oxide " terminology has become firmly established for the two compounds ethylene and propylene oxide, for more complicated substances, the epoxy method is to be preferred.

METHODS OF PREPARATION OF EPOXIDES

The direct attachment of oxygen to the double bond of an unsaturated hydrocarbon can take place ; Pigoulevski [2] showed that octene-1 is converted to 1, 2-epoxyoctane at 100° in the presence of traces of aldehyde (which appear to act through the formation of peroxides). When ethylene is passed with air over suitable catalysts at 200-350°, there is a partial conversion to ethylene oxide.

The oxidation of unsaturated hydrocarbons to their epoxides is one step in the formation of glycols from unsaturated compounds by the action of hydrogen peroxide, but it is unusual that the epoxide stage can be isolated. In the case of condensation products of aromatic aldehydes with aliphatic ketones, as in benzylidene acetone, the epoxide can be isolated in good yield :—



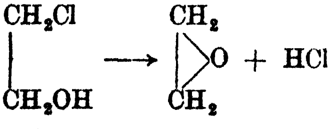
$$C_6H_5CHO + CH_3COCH_3 \rightarrow C_6H_5CH{=}CHCOCH_3 \xrightarrow{\text{oxidise.}} C_6H_5\overset{O}{CH\text{—}CH}COCH_3$$

For the isolation of good yields of epoxides from unsaturated hydrocarbons, the organic peroxides are particularly suited ; this reaction (often called by the name of Prileshaiev [3]) proceeds best with peracetic and perbenzoic acids, and may be summarised by the equation :—

$$C_6H_5CO\,.\,O\,.\,OH + C_2H_4 \longrightarrow C_6H_5COOH + C_2H_4O$$

The reaction has been used by Meerwein [4] as a means of investigating the influence of structure on the reactivity of unsaturated hydrocarbons. It should be added that some of the corresponding glycol is always produced with the epoxy compound, and appears to be formed by the addition of water to the epoxide. The reverse process constitutes a satisfactory method for the preparation of the epoxides ; heat alone, or the presence of an acid, is usually sufficient to induce the reaction, although the products are usually mixed with aldehydes or ketones produced by the isomerisation of the epoxide at the moment of liberation. This reaction is most successful with the aromatic glycols, and of the aliphatic compounds, those which undergo the reaction most readily are the pinacols, where some epoxide usually accompanies the pinacone produced in the pinacol-pinacone transformation.

One of the most successful methods for the preparation of epoxides is the removal of the elements of a halogen acid from a halohydrin. This reaction, summarised as



$$\begin{array}{l} CH_2Cl \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{l} CH_2 \\ |\rangle O \\ CH_2 \end{array} + HCl$$

---

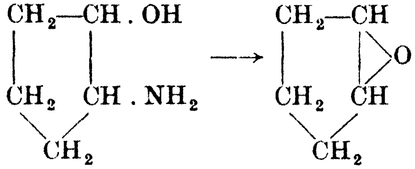
[1] Henry and Paget, *J.C.S.*, 1925, 1649.

[2] Pigoulevski, *J. Chim. Gen. Russe.*, 1934, **4**, 616.

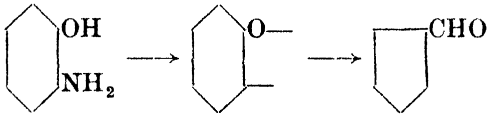
[3] Prileshaiev, *Ber.*, 1909, **42**, 4811.

[4] Meerwein *et al.*, *J. Pr. Chem.*, 1926, **113**, 9 ; 29.

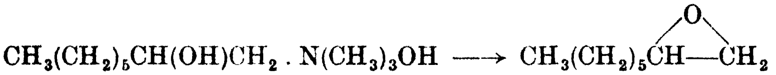
can be brought about by solid caustic alkalies, by their concentrated solutions, by strong ammonia and other bases. A very similar reaction is the simultaneous dehydration and deamination of α-aminoalcohols by nitrous acid. The reaction of nitrous acid on 2-amino*cyclo*pentanol, discovered by Godchot and Mousseron[1] is typical, and takes the following course :—



If an attempt is made to apply this method to 2-amino*cyclo*hexanol, then an extrusion reaction takes place with the formation of the aldehyde of *cyclo*pentane (this, incidentally, is the best way of obtaining this substance).



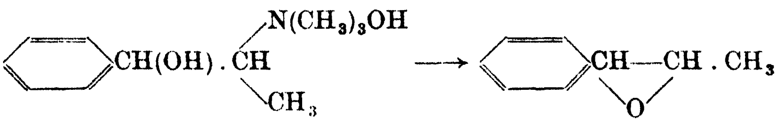
A similar reaction, of some considerable interest, is that developed by Späth in connexion with his work on the alkaloids, and which almost constitutes an extension of the method of exhaustive methylation. Thus, if a tetra-alkylammonium hydroxide in which one alkyl group carries a hydroxyl group β—to the nitrogen, is heated, trimethylamine or one of its analogues is evolved, together with water, and an epoxide remains. Späth, in his investigations on pseudoconhydrine[2] obtained 1, 2-epoxyoctane (245) by the action of heat on 2-hydroxyoctyl trimethyl ammonium hydroxide (244)



$$CH_3(CH_2)_5CH(OH)CH_2 . N(CH_3)_3OH \longrightarrow CH_3(CH_2)_5\overset{\diagup \!\! O \!\! \diagdown}{CH—CH_2}$$

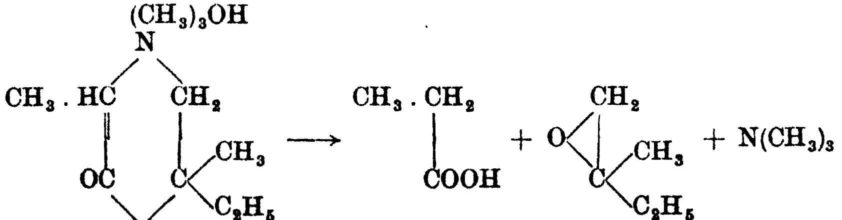
(244) (245)

The reaction is equally applicable to aralkyl compounds, as shown by the formation of 1-phenyl-1, 2-epoxypropane (247) by heating the quaternary methylamine hydroxide from ephedrine (246)



(246) (247)

Further, this process can be applied to cyclic compounds, as, for example, the morpholones. Thus, the quaternary hydroxide from dimethyl ethyl morpholone (248) yields 2-methyl-1, 2-epoxybutane (249) on heating :—



(248) (249)

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[1] Godchot and Mousseron, *C.R.*, 1934, **198**, 200.

[2] Späth *et al.*, *Ber.*, 1933, **66**, 591.

The most interesting physical characteristic of the epoxides is their extremely low boiling points, in comparison with those of the corresponding glycols, thus :—

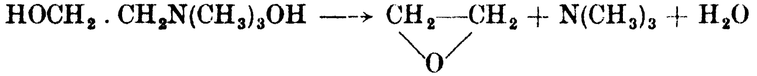
	Epoxide (B.P.)	Glycol (B.P.)
Ethane . . .	10·5°	197°
Propane . .	35°	189°
Butane . . .	64·5°	192°
Pentane . .	91°	205°
Hexane . .	119°	224°
Heptane . .	144°	240° (decomp.)

SOME INDIVIDUAL EPOXIDES

Ethylene Oxide.—When this compound was first prepared by Würtz in 1859, he regarded it as a " link between organic and mineral chemistry ",[1] on account of the fact that its speed of reaction with many inorganic substances resembles that of the bases. Thus, it unites instantaneously with dry hydrogen chloride and with acetic acid, and precipitates magnesia from solutions of magnesium salts. These reactions enabled Würtz to detect a parallel with ammonia.

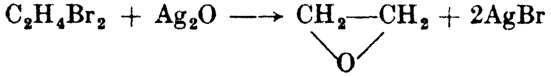
Apart from the methods which have already been mentioned for the preparation of ethylene oxide, the following are of interest :—

1. The action of heat on choline :—

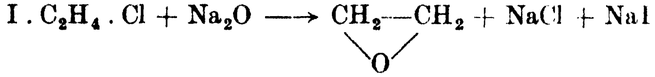


$$\mathrm{HOCH_2\,.\,CH_2N(CH_3)_3OH \longrightarrow \underset{\diagdown O \diagup}{CH_2{-}CH_2} + N(CH_3)_3 + H_2O}$$

2. The action of silver oxide upon ethylene dibromide, or of sodium oxide on the addition compound between ethylene and iodine monochloride :—



$$\mathrm{C_2H_4Br_2 + Ag_2O \longrightarrow \underset{\diagdown O \diagup}{CH_2{-}CH_2} + 2AgBr}$$



$$\mathrm{I\,.\,C_2H_4\,.\,Cl + Na_2O \longrightarrow \underset{\diagdown O \diagup}{CH_2{-}CH_2} + NaCl + NaI}$$

3. The action of bases on glycol chlorhydrin is the commonest laboratory method of obtaining the material in small quantities.

Industrially, ethylene oxide is prepared by the oxidation of mixtures of air and ethylene in the presence of catalysts ; considerable amounts are obtained during the production of glycol (*q.v.*), together with dioxane.

Ethylene oxide is a gas, condensing to a mobile liquid of ethereal odour at 10·5°. It is widely used (often as a mixture with nine times its weight of carbon dioxide) as a fumigant for foodstuffs, especially dried fruit and cereals. Such a mixture is adequate to deal with the disinfestation of grain and fruit, and leaves the material free from odour or toxic properties. Some ethylene oxide is used as a raw material in organic syntheses.

Würtz, in his original experiments on ethylene oxide, observed that it polymerised on standing to a white crystalline mass, m. 56°, and the formation of polyethylene glycols was explored by Lourenço a few years later ; he observed a series of polymers to which he ascribed the structures

Diethylene glycol	$HO\,.\,C_2H_4O\,.\,C_2H_4OH$	b. 250°
Triethylene glycol	$HO\,.\,(C_2H_4\,.\,O)_2C_2H_4OH$	b. 290°
Tetra-ethylene glycol	$HO\,.\,(C_2H_4\,.\,O)_3C_2H_4OH$	b. 230°/25 mm.
Penta-ethylene glycol	$HO\,.\,(C_2H_4\,.\,O)_4C_2H_4OH$	b. 281°/25 mm.
Hexa-ethylene glycol	$HO\,.\,(C_2H_4\,.\,O)_5C_2H_4OH$	b. 325°/25 mm.

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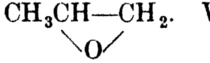
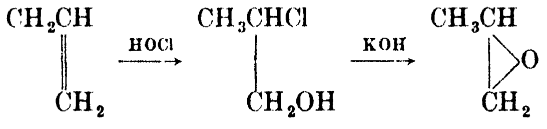
[1] Würtz, *J.C.S.*, 1862, **15**, 387.

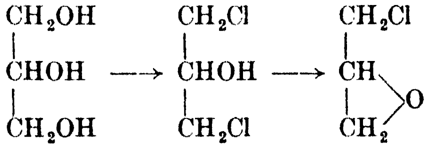
The polymer of Würtz appears to contain about thirty molecules of the oxide, while by the use of stannic chloride, polymers with a molecular weight up to 5000 are formed. Some of these polymers are wax-like solids, and are industrially valuable substances; the trade-name 'Carbowax' is used for the polymers of M.W. 1500-4000. The reactions of ethylene oxide are numerous and of great interest; many are associated with the opening of the oxide ring, although in others (a small minority) the ring remains intact. The principal reactions are shown in Table IX on page 340.

The name propylene oxide is usually given, not to the 1, 3- epoxide, but to the 1, 2- compound  $\underset{\diagdown O \diagup}{CH_3CH{-}CH_2}$. When propylene from cracker-gas is treated with hypochlorous acid propylene chlorhydrin is formed; this, in turn, on treatment with caustic alkali, gives propylene oxide



Industrially, propylene oxide is produced by the passage of air and propylene over a copper or silver catalyst, when a mixture of propylene oxide, propylene glycol and propanol is produced. Propylene oxide is a liquid boiling at 35°, and is capable of being separated into optically isomeric forms. Its reactions are very similar to those of ethylene oxide, although the various materials derived from it have not been so widely investigated.

The monochloro-derivative of propylene oxide, usually called epichlorhydrin (250) is probably the most widely encountered epoxide, after ethylene oxide itself. Discovered by Bertholet in 1856 by the action of alkalies on the mixed chlorhydrins from glycerol and hydrochloric acid, it is usually obtained by this process :—



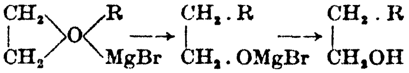
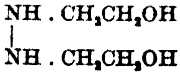
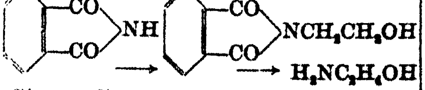
(250)

It is a mobile liquid with an odour reminiscent of chloroform, and is an excellent solvent for lacquers and resins; like propylene oxide, it can be separated into *dextro-* and *lævo-* forms. Chemically, epichlorhydrin shows mainly the reactions of the oxide ring, rather than of an active chlorine group. With water the monochlorhydrin is regenerated; with alcohol, the diethyl ether of glycerol monochlorhydrin is formed. The action of hydrogen cyanide and the halogen acids is very similar to their action upon ethylene oxide. Both the epibromohydrin and epiiodohydrin are known. Some of the properties of the more commonly encountered alkylene oxides are shown in Table X.

In addition to the aliphatic epoxides there are many cyclanic and aromatic examples of this series. The cyclane epoxides are subdivided into the three classes, nuclear, juxtanuclear and extranuclear. The chief nuclear epoxide is *cyclo*hexene oxide, or 1, 2-epoxy*cyclo*hexane (251). It may be obtained by stirring a suspension of *cyclo*hexene and mercuric oxide, and allowing chlorine slowly to bubble through the liquid. Hypochlorous acid is formed, and is immediately taken up by the *cyclo*hexene to form 2-chloro*cyclo*hexanol; this, on treatment with caustic soda solution, yields *cyclo*hexene oxide as a liquid b. 131°, with a very powerful odour.

TABLE IX

REACTIONS OF ETHYLENE OXIDE

Reagent	Conditions	Course of reaction
Sodium amalgam	Aqueous	Forms ethanol
Hydrogen	Ni at 125°	Forms crotonaldehyde in good yield
Air	Pt at 200°	Forms glycollic acid
Bromine		Forms ruby-red crystals of a compound, $(C_2H_4O)_2Br_2$, which is somewhat unstable (m. 65°) and gives dioxane when shaken with Hg
Hydrogen chloride Hydrogen bromide Hydrogen iodide	Cooled	The halohydrin is regenerated ; a method which is useful for making laboratory quantities of the bromohydrin and iodohydrin
Hydrogen cyanide	In ether	Yields hydracrylic nitrile $HO.C_2H_4CN$ (ethylene cyanohydrin)
Nitric acid	In cold H_2SO_4	Yields glycol dinitrate
Acetic acid		Gives a mixture of glycol mono- and diacetates
Acetic anhydride		Forms glycol diacetate and the acetates of the polyglycols
Water	In sealed tube	Regenerates glycol
Methyl Ethyl alcohols Butyl		Methyl Ethyl " Cellosolve ", which are the half ethers of glycol Butyl $HO . C_2H_4 . OR$ Valuable solvents
Glycol		Diethylene glycol
The cellosolves		The "carbitols", $HO.C_2H_4.O.C_2H_4.O.R$, where R is methyl, ethyl or butyl. Valuable solvents
Grignard reagents	In ether	Give addition compounds which rearrange to normal Grignard  compounds, giving primary alcohols, (see also p. 261)
Hydrogen sulphide	Alone	Gives thiodiglycol $(HO . C_2H_4)_2S$
Hydrogen sulphide	Aqueous	Gives monothioglycol, $HO . C_2H_4 . SH$
Ammonia		Yields the ethanolamines :— Mono- $NH_2 . CH_2 . CH_2OH$ Di- $NH(CH_2 . CH_2OH)_2$ Tri- $N(CH_2 . CH_2OH)_3$ Valuable wetting and emulsifying agents
Dimethylamine	Methanol at 40-50°	Dimethylaminoethanol
Diethylamine	Methanol at 40-50°	Diethylaminoethanol (for Procaine manufacture)
Hydrazine [1]	Aqueous	The compound :—  $\begin{array}{l} NH . CH_2CH_2OH \\ \vert \\ NH . CH_2CH_2OH \end{array}$
Phthalimide [2]		Enables the ethylene oxide to be converted entirely to mono-ethanolamine 
Aldehydes and ketones	$SnCl_4$	Give cyclic acetals, or dioxolones

---

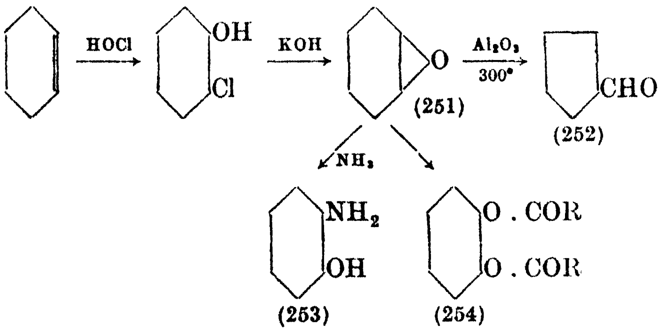
[1] Knott and Broundson, *Ber.*, 1902, **35**, 4474.
[2] Gabriel and Ohle, *ibid.*, 1917, **50**, 820.

TABLE X

SOME COMMON EPOXIDES

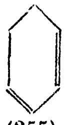
Name	Formula	B.P.	Properties, etc.
Ethylene oxide	C_2H_4O	12°	Mobile liquid
Propylene oxide	$CH_3 . C_2H_3O$	35°	Mobile liquid, chloroform odour
1, 3-Epoxypropane	$\underset{\diagdown O \diagup}{CH_2CH_2CH_2}$	48°	Miscible with water, pleasant odour
1, 2-Epoxybutane	$\underset{\diagdown O \diagup}{CH_3CH_2CH . CH_2}$	65°	
2, 3-Epoxybutane	$\underset{\diagdown O \diagup}{CH_3CH . CH . CH_3}$	54° 60°	*cis*- $(d)_{20}$ 0·8053 *trans*- $(d)_{20}$ 0·8272
1, 1-Dimethyl ethylene oxide	$\underset{\diagdown O \diagup}{(CH_3)_2C—CH_2}$	ca 55°	From the chlorhydrin
1, 2-Epoxypentane	$\underset{\diagdown O \diagup}{CH_3(CH_2)_2CH—CH_2}$	91°	Action of potash on 2-chloro hexanol-1
iso-Propylethylene oxide	$\underset{\diagdown O \diagup}{(CH_3)_2CH . CH—CH_2}$	82°	Potash on the product of HOCl on *iso*-propylethylene
2, 3-Epoxypentane	$\underset{\diagdown O \diagup}{CH_3CH_2CH—CH . CH_3}$	80°	
1, 2-Epoxyhexane	$\underset{\diagdown O \diagup}{CH_3(CH_2)_3CH—CH_2}$	119°	
1, 2-Epoxyheptane	$\underset{\diagdown O \diagup}{CH_3(CH_2)_4CH—CH_2}$	144°	From perbenzoic acid and heptene-1
1, 2-Epoxyoctane	$\underset{\diagdown O \diagup}{CH_3(CH_2)_5CH—CH_2}$	158°	From perbenzoic acid and octene-1
1, 2-Epoxyhexadecane	$\underset{\diagdown O \diagup}{CH_3(CH_2)_{13}CH—CH_2}$	m. 22 ;	b. 177°/12 mm. From heating tetradecylcholine

The reactions of *cyclo*hexene oxide resemble, in many ways, those of ethylene oxide, but, in addition, the compound has a strong tendency to pass into *cyclo*pentane aldehyde (252), a reaction which may be completed by passing the vapour over alumina heated to 300°. When warmed with acids, or their



anhydrides, *cyclo*hexene oxide is converted to the *di*-acyl derivative of the 1, 2-glycol (254), and on treatment with aqueous ammonia the aminoalcohol (253) is formed.

When *cyclo*hexadiene (255) is treated with perbenzoic acid, the *di*-epoxide (256) is obtained, which is a liquid, b. 66°/11 mm. ; with benzene, of course, no trioxide is obtainable, although it is possible that such a compound may be one stage in the decomposition of benzene triozonide. Several mono-epoxides have been obtained from seven and eight membered unsaturated rings; thus,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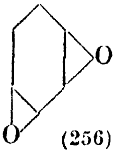

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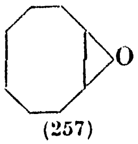
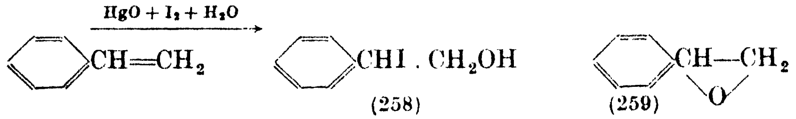


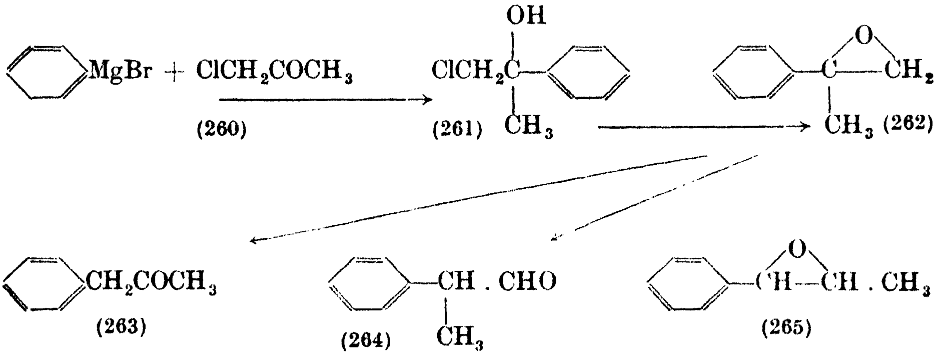
(257)

epoxy*cyclo*öctane (257) is a crystalline compound, m. 45°, which boils without undue decomposition at 190°.

The simplest aryl epoxide is styrene oxide (259), a liquid, b. 192°, obtained by the action of alkali on styrene iodohydrin, in turn, obtained from styrene itself by the action of mercuric oxide and iodine (258). One of the more

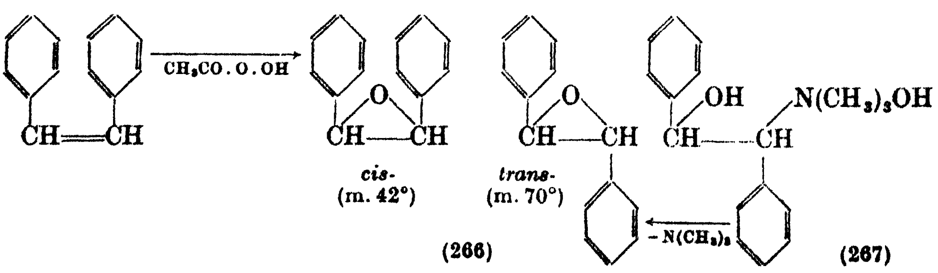


interesting aromatic epoxides is the methyl analogue of the previous substance, 1-methyl-1-phenylethylene oxide. The synthesis of this compound commences with the action of phenyl magnesium bromide on chloroacetone (260), when the chlorhydrin (261) of the required epoxide is obtained. This, on treatment with alkali, yields the epoxide (262), which, upon distillation at ordinary

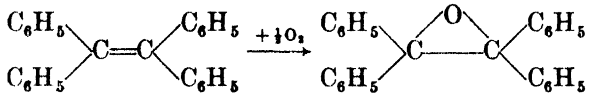


pressures isomerises to hydratropic aldehyde (264); with concentrated sulphuric acid at — 15°, it yields phenyl acetone (263). The isomeric 1-methyl-2-phenyl ethylene oxide (265) exists in two geometrically isomeric forms (α- and β-), both of which can be resolved into optically active pairs.

s-Diphenyl ethylene oxide (266) also exists in *cis*- and *trans*- forms, although they are optically homogeneous; the *cis*- form is obtainable by the peracetic acid oxidation of *iso*-stilbene; the *trans*- form may be obtained from diphenyl choline (267).



The intensely stable tetraphenyl ethylene oxide (269) can be obtained either by the oxidation of tetraphenylethylene (268) with perbenzoic acid, or by the dehydration of benzpinacol (270).



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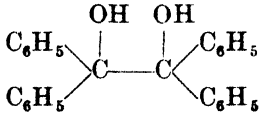
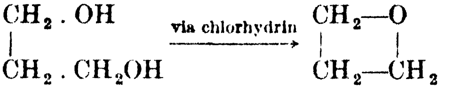


(270)

THE FURANS

The tendency of glycols to form an internal ether or epoxide, continues with the longer stems, and as the number of carbon atoms increases, a change in ease of formation of the epoxide is noted. Thus, trimethylene oxide (1, 3-epoxypropane) (271) is most difficult to obtain from the glycol by direct means —a fact reminiscent of the difficulties of *cyclo*-butane formation ; on the other hand, the formation of five and six membered epoxide rings proceeds with ease, and the process is irreversible ; once the epoxide is formed it shows little tendency to pass back again to the glycol. Thus, when butane diol, 1-4 is heated with 60 per cent. sulphuric acid, 1-4 butylene oxide is formed, better known as tetrahydrofuran (272), b. 67°, since it is the parent structure of the widely distributed furan family. This tendency towards the formation of a stable ring is shown also by pentamethylene glycol (273), but higher glycols suffer rearrangement before ring closure takes place, for when tetradecamethylene glycol is heated with 60 per cent. sulphuric acid, 2-nonylpentamethylene oxide results (274).



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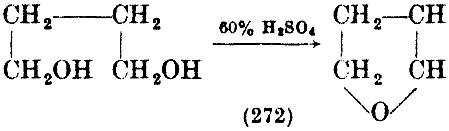

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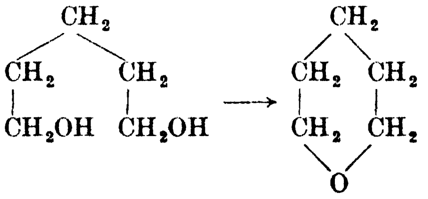

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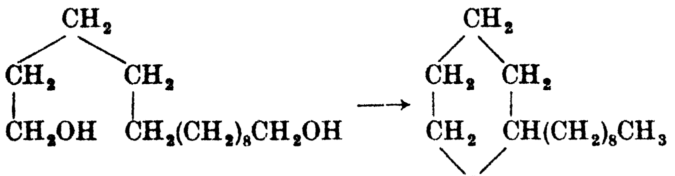

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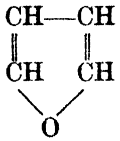


(275)

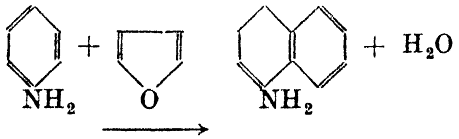
Although tetrahydrofuran is a comparatively stable substance, it is surpassed in stability by furan itself (275), which contains two double bonds, and which should, at first sight, be a particularly unstable substance. On the contrary, however, it has a considerable degree of stability and, in addition, some of the attributes of aromatic character.

Furaldehyde is the derivative of furan most commonly met with ; it was first prepared by Döbereiner in his attempts to obtain formic acid by the oxidation of sugar with manganese dioxide and dilute sulphuric acid. Some furaldehyde, distilled as an oil, which Döbereiner called "artificial oil of ants"[1]; Stenhouse[2] obtained better yields by using flour or sawdust as a raw material, but it remained for Fownes,[3] in 1845 to obtain considerable quantities of furaldehyde, which he did by distilling bran with dilute sulphuric acid; he named the new liquid 'furfurol' from 'furfur', the onomatopœic Latin word for 'bran', and 'oleum' = 'oil'. The 'ol' termination being reserved for alcohols, 'al' has been substituted, and 'furfural' has been commonly employed to name this compound; since the name is used as a root for all compounds of the class, the duplicated first syllable is often omitted 'fural' or, more commonly, 'furaldehyde' being used.

Furan itself was first prepared by Limpricht[4] in 1870 by distilling barium pyromucate with soda-lime; the discoverer of this compound regarded it as a phenolic derivative from a hypothetical C_4H_4, and named it 'tetraphenol'. Baeyer recognised its true structure and also its relation to furaldehyde.

Furan occurs in wood-tars, and because of its low b. pt. (32°), can be isolated readily by fractionating the forerun of the distillation of such tars.

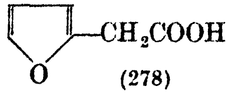
Furan is a colourless mobile liquid with an odour as of chloroform; it is unaffected by sodium or caustic alkali, but polymerises instantly and explosively in the presence of traces of hydrochloric acid. One of the most interesting reactions of furan is its direct condensation[5] with aniline (276) to give α-naphthylamine (277).



(276) (277)

The reduction of furan is not readily accomplished; even palladium and hydrogen require a high temperature and pressure. Further, halogens substitute, and do not add to, furan; thus 2, 5-dibromofuran is obtained from furan by the direct action of bromine, and may be hydrolysed to maleic acid. Furan vapour reacts with ammonia or hydrogen sulphide when passed with either over alumina at 450°, giving pyrrole or thiophen. When furan vapour comes into contact with a pine-shaving soaked in hydrochloric acid, a green colour is obtained. The α-methyl analogue of furan (sylvan) is found in wood tars, and may be fractioned from the forerun of the tars mentioned above. It is a liquid, b. 63°, which resembles furan in many ways. 2, 5-Dimethylfuran, b. 94°, also accompanies furan in wood tars, and may also be separated from the products obtained when sucrose is distilled with lime.

Certain anomalies exist in respect of the nomenclature of derivatives of furan; thus the group (280) as in furylacetic acid is referred to as the 'furyl' group; but the group (281) as in furfuryl alcohol (279) is the 'furfuryl' group.



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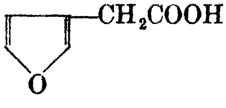

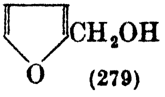

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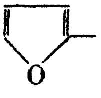
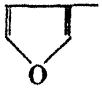
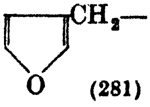


α-furyl

(280)



β-furyl



(281)

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[1] Döbereiner, *Schweigg. Journal*, 1831, **68**, 368.

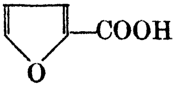
[2] Stenhouse, *Phil. Mag.*, 1841 [3], **18**, 122; 1850, **37**, 226.

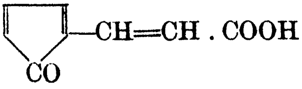
[3] Fownes, *Phil. Trans.*, 1845, **135**, 253.

[4] Limpricht, *Ber.*, 1870, **3**, 90.

[5] Oliveri and Canzoneri, *ibid.*, 1887, **20**, 220.

On the other hand, pyromucic acid, now more generally known as furoic acid (282), contains the α-furoyl group (284). The group (285) is termed the 'fural' group; thus, compound (283) has been called 'α-furalacetic acid', alternatively 'α-furylacrylic acid'. The anomaly lies in the fact that most of the group names, e.g. fural, furoyl, are the equivalents of the similar word with the first syllable duplicated, as in furfural, and furfuroyl; in one instance, however, this is untrue—'furyl' and 'furfuryl' are not equivalent—the latter being a homologue of the former. This is apparent in considering the names of the compound (286), which is α-furyl propionic acid, or α-furfuryl acetic acid. This anomaly is confusing, and can be overcome by abandoning the use of 'furfuryl'; the only difficult case is that of 'furfuryl alcohol' (287), which can easily be termed 'furyl carbinol'.


α-furoic acid
(282)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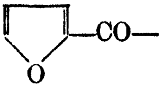
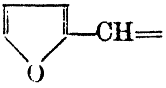

α-furoyl
(284)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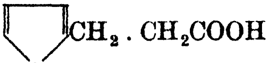
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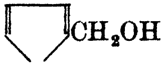
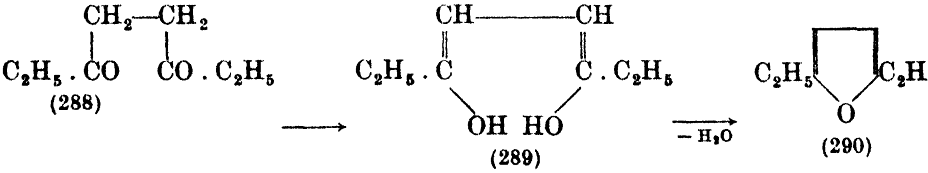
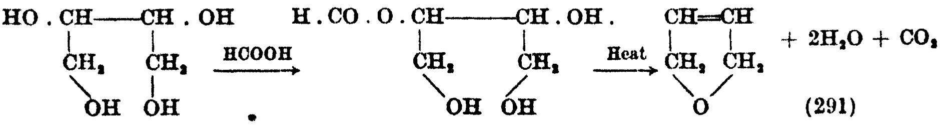
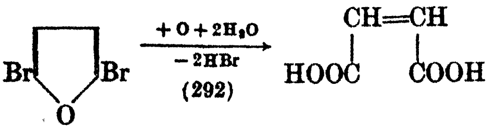

(287)

One of the most prolific methods of synthesing furan derivatives is from substances showing a 1, 4-diketo structure. Thus, octanedione-3, 6 (288) is readily dehydrated in its dienolic form (289) to αα'-diethylfuran (290). Dihydrofuran (291) is obtained by heating erythritol with 80 per cent. formic acid to 200-210°; a reaction which appears to take the course :—

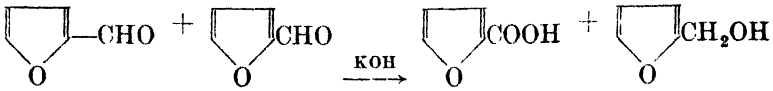




Dihydrofuran is a colourless liquid, b. 67°, which is, unlike furan itself, indifferent to acids and alkalies. The action of bromine on furan gives the 2, 5-dibromo derivative, an oil boiling at 165°. Its most interesting reaction is its conversion to maleic acid (292) by the combined action of air and water.

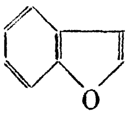


Furyl Carbinol (*Furfuryl Alcohol*).—This compound occurs naturally in clove oil, and is found in the oil from roasted coffee, together with the corresponding mercaptan and their thienyl analogues. It can be obtained either by the reduction of furaldehyde or by the Cannizzaro reaction with furaldehyde and dilute aqueous alkalies.

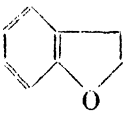


Industrially, the bulk of furyl carbinol is obtained by the catalytic reduction of the aldehyde; it is accompanied by tetrahydrofuryl carbinol, since the nucleus is reduced as well as the side-chain. Furyl carbinol and its tetrahydro derivative are similar in general properties but can be separated by fractional distillation. They are miscible with water and organic solvents, and are utilised as solvents for lacquers and varnishes.

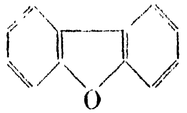
Numerous fused-ring compounds derived from the furan series are known including :—



(293)
Coumaron



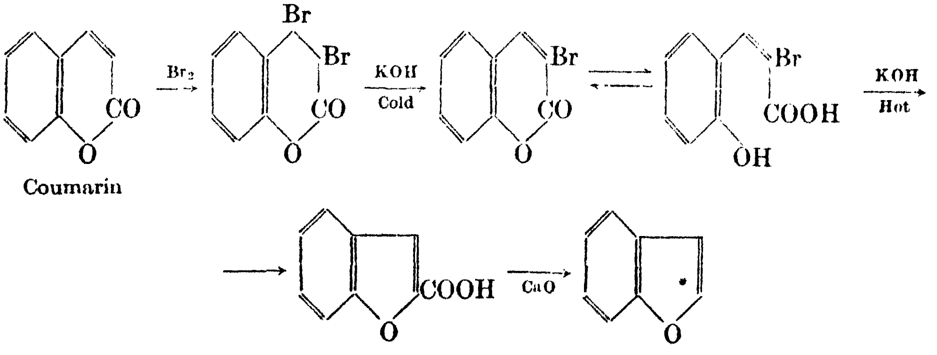
(294)
Coumaran



(295)
Diphenylene oxide

Coumaron and coumaran were both unfortunately named: the former as "coumarone" is not, as the last syllable of the name should connote, a ketone, nor is "coumarane" a saturated hydrocarbon. The alternative names benzfuran and dihydrobenzfuran are to be preferred, especially in view of the fact that coumarin is the accepted name of a different type of ring.

Coumaron (benzfuran) was first prepared in 1883 by heating coumarilic acid (296) with lime. The loss of carbon dioxide leads to the formation of coumarone (297), which has also been found with indene in the fraction of coal-tar naphtha boiling between 168° and 175°. Coumarilic acid is obtained from coumarin by the process outlined in the formulæ below :—



Coumarin

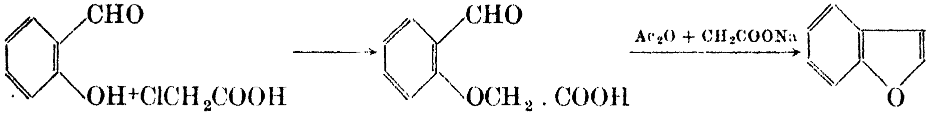
(296) (297)

Coumaron may also be obtained direct from coumarin by passing the vapour of the latter substance[1] through a tube heated to 850°. Other methods by which the parent member of this family may be obtained are from [2] salicylaldehyde and chloroacetic acid (298), which when melted together form a resin

[1] Fittig and Ebert, *Ann.*, 1883, **216**, 162.

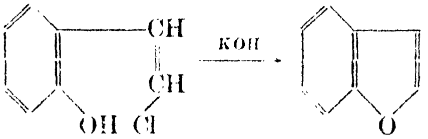
[2] Rössing, *Ber.*, 1884, **17**, 3000.

which, on extraction with alkali and reprecipitation with hydrochloric acid, gives the aldehydophenoxyacetic acid (299); this, when heated with acetic acid and acetic anhydride, is cyclised by an intramolecular Perkin reaction,



(298) (299) (300)

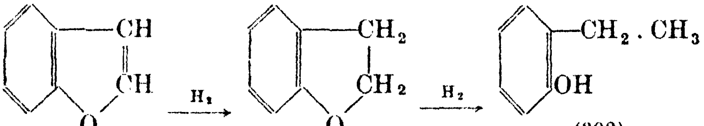
at the same time losing carbon dioxide and forming coumaron (300). Komppa[1] prepared coumaron by the loss of the elements of hydrogen chloride from *o*-hydroxy-ω-chloro-styrene (301).



(301)

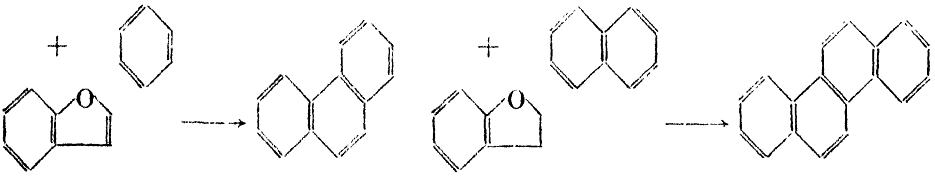
Coumaron is a colourless liquid, b. 173°—the properties of which resemble those of furan in many ways, particularly in its ability to polymerise into resins in the presence of traces of acids. The resins ('coumarone resins') are valuable as varnish bases, and are used industrially.

Coumaron is reactive; on reduction it gives an excellent yield of *o*-ethylphenol, coumaran being formed as an intermediate stage (302).



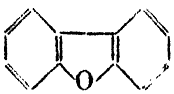
(302)

The interesting researches of Kramer and Spilker[2] have shown that when benzene and coumaron vapours are passed through a red-hot tube, phenanthrene is produced in good yield, and that other hydrocarbons behave similarly, naphthalene giving chrysene:—



It is probable that the presence of these hydrocarbons in coal-tar is accounted for by this reaction.

Many coumaron derivatives are found in nature, and constitute a large group of fish and insect poisons investigated by E. Späth. An account of some of these is given in Chapter VII, in connexion with the lactones.



(303)

Diphenylene oxide (303) is best prepared by distilling a mixture of phenol and lead oxide; phenol and diphenylene oxide pass over and may be separated by taking advantage of the insolubility of the oxide in aqueous alkali. It is also obtained in small quantities in the tars of many destructive distillations, especially of carbohydrate materials, and has been found in fair quantity in 'stuppfett'. This latter material warrants a short description, as it appears in the literature as the source of many aromatic hydrocarbons. When the mercurial ores of Idria were smelted, the mercury passed over, together with a black plastic mass—or 'stupp'. This 'stupp' still contained much mercury which could not be separated by mechanical means and was, therefore, redistilled; mercury passed over, together with a crystalline oily mass, the 'stuppfett'. This was a mixture of hydrocarbons from which Goldschmidt and Schmidt[1] isolated the following:—

---

[1] Komppa, *Ber.*, 1895, **28**, 2986.

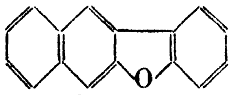
[2] Kramer and Spilker, *ibid.*, 1890, **23**, 84.

	Per cent.
Phenanthrene	45
Pyrene	20
Fluoranthrene	12
Naphthalene	3
Chrysene	2-3 per cent. each.
Anthracene	
Methylnaphthalene	
Ethylnaphthalene	
Acenaphthene	
Diphenyl	
Diphenylene oxide	
Quinoline	

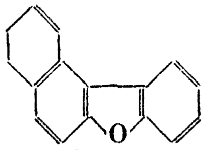
It is more than sixty years since 'stuppfett' was obtained at Idria, but examination of its hydrocarbons led to the recognition of several structures which had not previously been observed.

Diphenylene oxide is a solid, crystallising in plates, m. 81°, b. 288°, and is extremely inert.

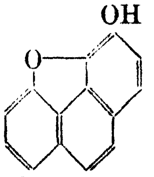
Among the more complex fused rings of the furan group are the brazans and morphenol. β-Brazan has been separated from the higher coal-tar fractions by chromatographic adsorption.[2] It is also obtained by a complex rearrangement of brazilin on heating with reducing agents; it is not directly related structurally to brazilin. β-Brazan forms white plates, m. 202°. β-Brazan was synthesised by Kostanecki and Lampe in 1908[3] from 3-hydroxybrazanequinone (306), previously obtained by Liebermann[4] by the condensation of resorcinol (305) with 2, 3-dichloro-α-naphthoquinone (304).



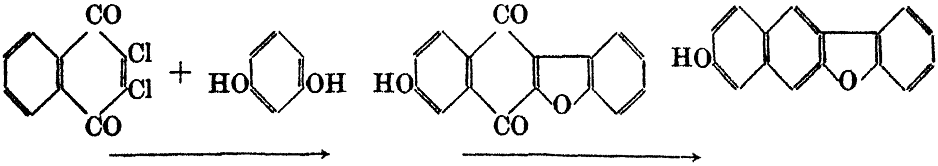
β-brazan



δ-brazan



Morphenol



(304) (305) (306) (307)

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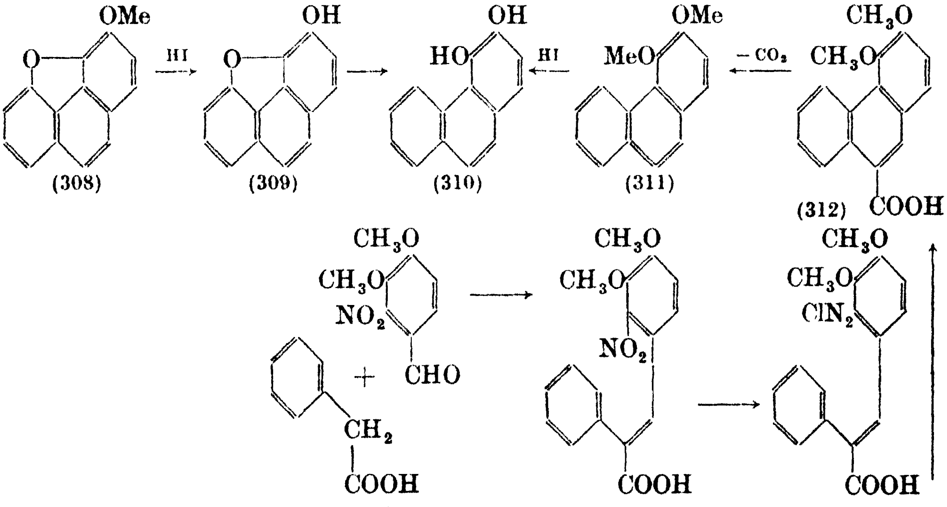
[1] Goldschmidt and Schmidt, *Monats.*, 1870, (2), **2**. 1 *Ber.*, 1877, **10**, 2022.
[2] Winterstein *et al.*, *Z. Physiol. Chem.*, 1934, **230**, 158.
[3] Kostanecki and Lampe, *Ber.*, 1908, **41**, 2373.
[4] Liebermann, *ibid.*, 1899, **32**, 924.

When hydroxybrazanquinone is reduced with hydriodic acid, hydroxy β-brazan (307) is formed, and from this β-brazan itself may be obtained by distillation with zinc dust.

Morphenol and its simple derivatives were noted as breakdown products from the morphine group of alkaloids over sixty years ago,[1] but so little was then known about the structure of phenanthrene, that it was impossible at that time to attach a structural formula to the compounds, and two decades passed before the significance of their relation to the alkaloids was realised. Morphenol, a white crystalline compound, m. 145°, is obtained as its mono-methyl ether (308) by the acid decomposition of α-methylmorphimethine (see Vol. II), which is readily demethylated to morphenol itself.

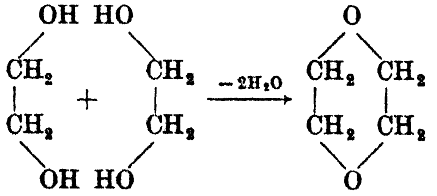


(308) (309) (310) (311) (312) (313) (314) (315)

Morphenol (309) yields phenanthrene on heating with selenium and 3, 4-dihydroxyphenanthrene (310) on treatment with sodium. This dihydroxy derivative (morphol) has been synthesised by the process indicated in formulæ (311) to (315). Since morphenol contains an ether link and a free hydroxyl group, its relation to morphol leads to the acceptance of its constitution as 3-hydroxy-4, 5-epoxyphenanthrene (309).

Some Cyclic Ethers

Apart from the epoxides and simple polymethylene ethers, which have already been discussed, there exists an important group of cyclic ethers comprising dioxan, trioxymethylene and paraldehyde in which two or more ether oxygen atoms are present in the ring. Casual references to the formation of dioxan (316) as a by-product in the manufacture of glycol have already been made ; when the quantities obtained in this way are insufficient for industrial needs, dioxan can be obtained by heating ethylene glycol with a little sulphuric acid, under pressure.



(316)

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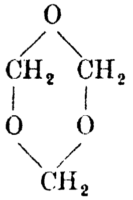
[1] Vongerichten and Schrötter, *Ber.*, 1882, **15**, 1484.

Dioxan (316), m. 9°, b. 102°, is a colourless, slightly viscous liquid which is miscible with water in all proportions; it has very valuable solvent properties, but on account of its toxicity, great care must be exercised in its use in bulk. Its solvent properties and low melting point (9°) make dioxan an excellent substance for the determination of molecular weights by cryoscopy. With water, dioxan forms an azeotrope, b. 87°, of the approximate composition, $C_4H_8O_2$, H_2O. Chemically the oxygen atoms of dioxan are remarkably active, having a strong tendency towards the formation of oxonium compounds; thus crystalline double compounds containing the oxonium structure are formed with mercuric chloride and bromide, with halogens and halogen acids, and with many substances such as iodoform.

TRIOXYMETHYLENE (TRIOXAN)

For many years the so-called 'paraformaldehyde', first obtained by Butlerow[1] in 1859, was regarded as a trimeric substance analogous to paraldehyde, and was frequently depicted in text-books as trioxymethylene (317) an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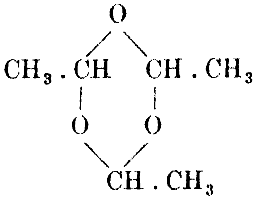
(318)

error which appears to have originated with Hofmann[2] in 1869. Paraformaldehyde was shown by Staudinger and Sauter to consist of a mixture of hydrated linear polymers of formaldehyde and to have the structure $HOCH_2(OCH_2)_nCHO$. Pratesi,[3] in 1885, obtained trioxymethylene (better known as 'trioxan') by heating paraform with a trace of sulphuric acid in sealed tubes at 115°. The cooler part of the tube at the upper end became filled with a mass of sublimed crystals of trioxan; various improvements in the methods of preparing trioxan have been made from time to time, but the experiments of Frank[4] showed that it was possible to obtain trioxan in bulk quantities by distilling a 60-65 per cent. solution of formaldehyde in water with 2 per cent. of sulphuric acid. The aqueous distillate is continuously extracted by methylene chloride, by which means the trioxan may be removed and recovered by distillation.

Trioxan is a colourless crystalline solid, m. 61-62°, b. 115°, boiling without decomposition. It has a pleasant odour, somewhat like chloroform; the acid odour of formaldehyde is quite absent. Like dioxan, trioxan is capable of forming an azeotrope with water which contains 30 per cent. of the latter component and distils at 91·5°. Crystals of trioxan are capable of being bent without fracture, and have a strong electrical polarity. One end of a long crystal will discharge an electroscope when presented to the plate.

Chemically, this trimer is characterised by stability, and in many respects resembles dioxan. It neither hydrolyses nor depolymerises in aqueous solution, and needs boiling for five hours with 2 per cent. sulphuric acid to regenerate formaldehyde to the extent of 50 per cent. Heated dry with traces of strong acids or of zinc chloride, the depolymerisation is complete, anhydrous formaldehyde being produced. In the presence of an acceptor, this formaldehyde reacts most readily, and since the trioxan is itself soluble in many organic solvents, formaldehyde reactions can be accurately controlled in a single phase, which is not possible with gaseous formaldehyde or paraformaldehyde. A similar degree of control can be made in the polymerisation of phenol-formaldehyde mixtures. Phenol-trioxan mixtures at 70° in the presence of one part in ten thousand of sulphuric acid polymerise steadily to transparent solids.

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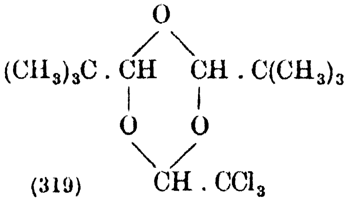
[1] Butlerow, *Ann.*, 1859, **111**, 242.

[2] Hofmann, *ibid.*, 1868, **145**, 357.

[3] Pratesi, *Gazz. Chim. Ital.*, 1885, **14**, 139.

[4] U.S.P. 2,304,080 (1942), C. E. Frank (to E. I. duPont & Co.).

The homologous paraldehyde (*s*-trimethyltrioxan) (318) is obtained by the action of a trace of sulphuric acid on aldehyde. It is a liquid, b. 124°, and is a useful soporific. One of its advantages is that unlike many sedative drugs, it acts during the cerebral excitement engendered by continual alcoholic excess. It has a nauseous taste. Chemically it resembles trioxan in many ways, but is more readily depolymerised, dilute sulphuric acid being capable of effecting this process at 50°. Hibbert showed that mixed substituted trioxans can be obtained by allowing mixtures of aldehydes to stand in the presence of a trace of sulphuric acid; an example (319) is obtained by the condensation of two moles of trimethylacetaldehyde and one of chloral.


(319)

APPENDIX I

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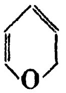
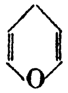
APPENDIX II

PYRONES AND PLANT PIGMENTS

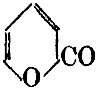
The parent rings of the whole family of plant pigments are the pyrans. Neither α- nor γ-pyran have been isolated, but the corresponding α- and γ-pyrones are known



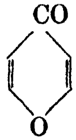
α-pyran



γ-pyran



α-Pyrone

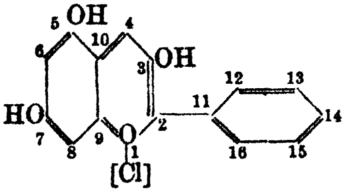


γ-Pyrone

From γ-pyran are derived the anthocyanins, and from the pyrone structures, the flavones and chromones arise.

The anthocyanins are glycosides obtained from the flowers and fruit of plants, and they constitute the bulk of the red, blue and violet pigments found in vegetable sources. Thus, the cornflower owes its blue colour to cyanin, which occurs to the extent of 0·75 per cent. in the dried petals ; dark coloured flowers such as black pansies contain as much as 33 per cent. of anthocyanin, whilst the dark red dahlias (e.g. ' Bishop of Llandaff ') contain up to 20 per cent.

Nearly all the anthocyanins appear to be glycosides derived from the structure 3, 5, 7-trihydroxy-2-phenylbenzpyrylium chloride (319). The main



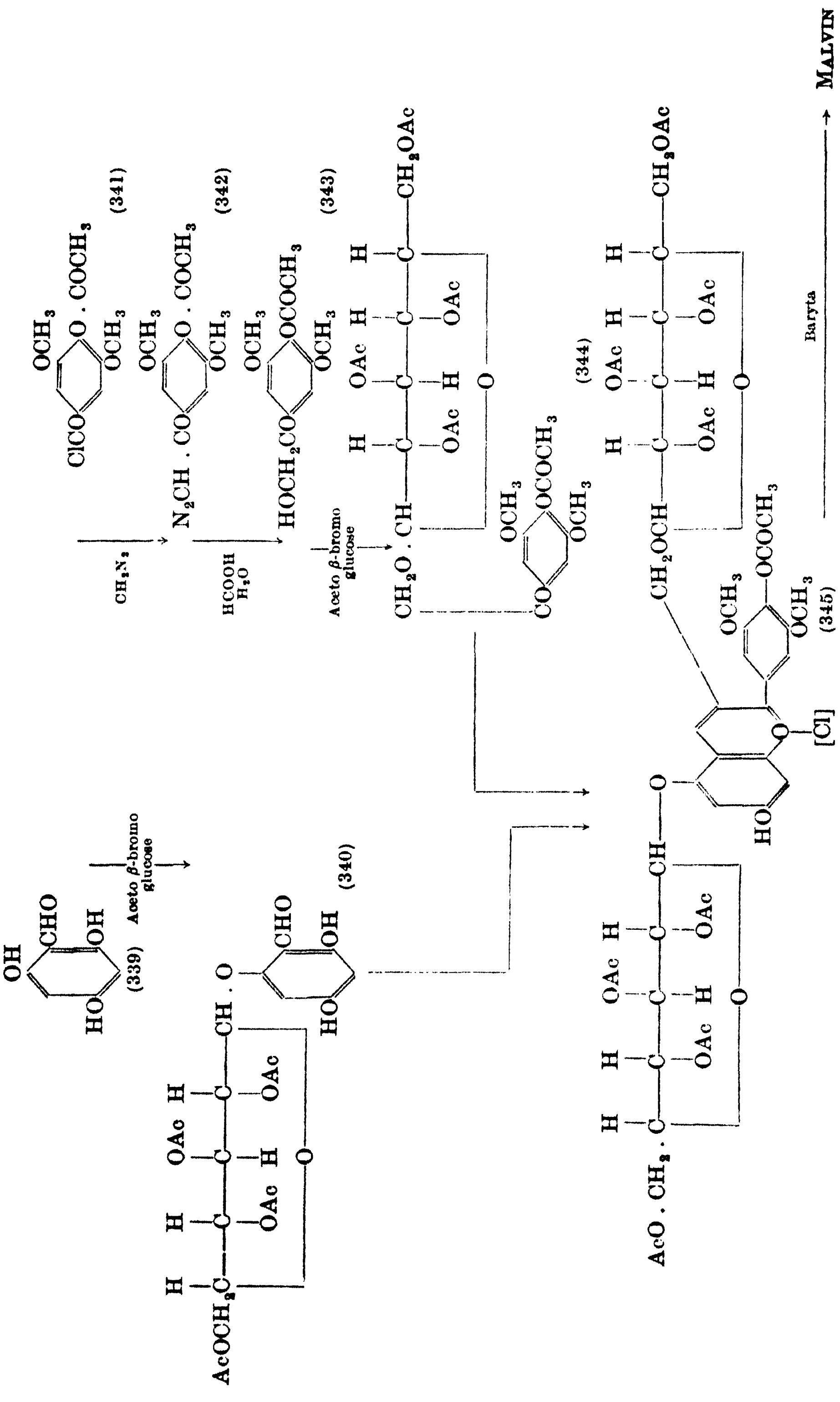
(319)

14-OH	Pelargonidin
13, 14-di OH	Cyanidin
13, 14, 15-tri OH	Delphinidin

TABLE XI

SOME ANTHOCYANINS

Name	Aglycone	Other Components	Source
Callistephin	Pelargonidin	3-Glucoside	Red Aster (*Callistephus sinensis*) Clove carnation (*Dianthus caryophyllus*)
Fragarin	Pelargonidin	3-Galactoside	Strawberry (*Fragaria*)
Gloxinin	Pelargonidin	3-Rhamnoglucoside	Scarlet *Gloxinia*
Punicin	Pelargonidin	3-Diglucoside	Pomegranate (*Punica granatum*)
Pelargonin	Pelargonidin	3, 5-Diglucoside	Geranium (*Pelargonium zonale*) Dahlia (*D. variabilis*) Pink cornflower (*Centaurea*) *Gladiolus* (scarlet)
Salvianin Monardœin	Pelargonidin	2 mols. glucose + 2 mols. malonic acid + 1 mol. *p*-hydroxycinnamic acid	Salvia (*S. Splendeus*) Golden Balm (*Monarda didyma*)
Chrysanthemin Asterin Sambucin	Cyanidin	3-Glucoside	Chrysanthemum (*C. Indicum*) Red Aster (*Callistephus sinensis*) Blackberry (*Rubus fruticosus*) Elderberry (*Sambucus niger*)
Idæin	Cyanidin	3-Galactoside	Cowberry (*Vaccinium vitis-idœa*)
Antirhinin Keracyanin Prunicyanin	Cyanidin	3-Rhamnoglucoside	*Antirrhinum* Sweet cherry (*Prunus avium*) Sloe (*P. Spinosa*)
Mecocyanin	Cyanidin	3-Gentiobioside	Poppy (*P. Rhœas*)
Cyanin	Cyanidin	3, 5-Diglucoside	Dahlia, Pansy, Cornflower and Rose
Oxycoccicyanin	Peonidin (Cyanidin 13-methyl ether)	3-Glucoside	Cranberry (*Vaccinium oxycoccos*)
Peonin	Peonidin	3, 5-Diglucoside	Red Peony (*P. Officinalis*)
Vicin I and II	Delphinidin	3-Glucoside + 3-Rhamnoside	Vetch (*Vicia*). A mixture
—	Delphinidin	3, 5-Diglucoside	Blue salvia (*S. Patens*)
Gentianin	Delphinidin	Glucose + *p*-hydroxy cinnamic acid	Gentian (*G. Acaulis*)
Violanin	Delphinidin	Glucose + rhamnose + *p*-hydroxycinnamic acid	Black Pansy (*Viola tricolor*)
Delphinin	Delphinidin	2 mols. glucose 2 mols. *p*-hydroxybenzoic acid	Larkspur (*Delphinium consolida*)
Ampelopsin	Ampelopsidin (14-Methyl delphinidin)	3-Glucoside	*Ampelopsis quinquefolia*
Myrtillin	Myrtillidin (? Methyl-delphinidin)	3-Glucoside	Bilberry (*Vaccinium myrtillis*)
Petunin	Petunidin (? Methyl-delphinidin)	Glucoside	Petunia (*P. hybrida. hort.*)
Œnin (Primulin)	Malvidin (Delphinidin 13, 15-dimethyl ether)	3-Glucoside	Black Grape (e.g. Homburg) (*Vitis vinifera*) Primulas (*Polyanthus section*)
Malvin	Malvidin	3, 5-Diglucoside	Cyclamen Mallow (*Malva sylvestris*) Primulas (*P. viscosa* and *P. integrifolia*
Hirsutin	Hirsutidin (7, 13, 15- Tri methyl delphinidin)	3, 5-Diglucoside	Primulas (*P. Hirsuta*)
Gesnerin	Apigenidin (5, 7, 14-tri-hydroxy-2-phenylbenz pyrylium chloride)	Monoglucoside	*Gesnera Fulgens*



Robinson's Synthesis of Malvin

Robinson[1] proceeded still further and synthesised the anthocyanins malvin, pelargonin, cyanin, chrysanthemin and œnin. The synthesis of malvin is typical, and involves the following steps :—

(1) Acetylsyringoyl chloride is converted to an ω-diazo compound by diazomethane (341 and 342).
(2) With aqueous formic acid this is converted to the trisubstituted derivative of ω-hydroxyacetophenone (343).
(3) This substance yields a glycoside with β-bromoacetylglucose (344).
(4) A glycoside is prepared (340) from phloroglucin aldehyde (339) and β-bromoacetyl glucose.
(5) The two glycosides are condensed together to give acetylmalvin chloride which gives malvin (identical with the natural product) on deacetylation with baryta (345).

TABLE XII

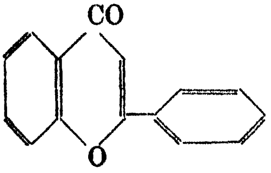
Reactions of Some Anthocyanidins

	TEST			
	I	II	III	IV
	Add 10 % NaOH and shake in air	Extract with amyl alcohol; add sodium acetate and trace of ferric chloride to extract	Distribution between 1 % HCl . Aq and 5 % picric acid in anisole/ethyl *iso*amyl ether (5 : 1)	Distribution between 1 % HCl . Aq and *cyclo*-hexanol/toluene (1 : 5)
Petunidin . .	Destroyed	Pure blue	Slightly extracted	Not extracted
Delphinidin .	Destroyed	Pure blue	Not extracted	Not extracted
Cyanidin . .	Stable	Pure blue	Some extracted	Pale rose
Pelargonidin .	Stable	—	Completely extracted	Extracted
Peonidin . .	Stable	—	Completely extracted	Extracted
Malvidin . .	Stable	—	Completely extracted	Faint blue

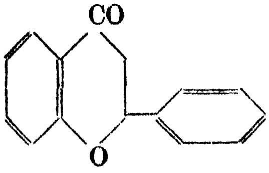
In Table XII a few of the distinguishing reactions of the anthocyanidins are set out. It is emphasised that the colour exhibited by an anthocyanin present in flowers depends on the pH of the plant fluids. Thus, the colour of the red rose and the cornflower, so obviously different, are due to the same anthocyanin, cyanin ; in the rose the pH is approximately 4, in the cornflower 10-11.

The Flavones

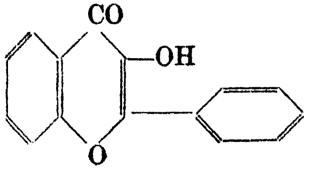
There are three main divisions into which plant pigments of the flavone group fall, according to whether they are derived from the flavone, flavanone or flavonol structures.



Flavone



Flavanone



Flavonol

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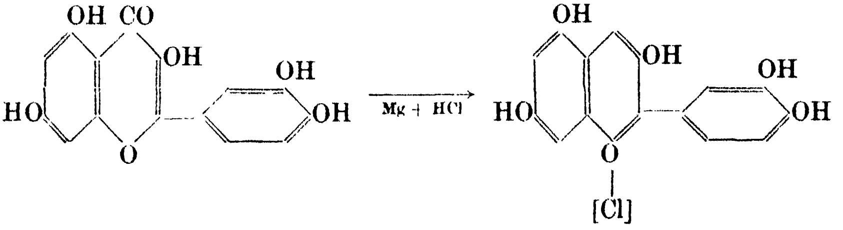
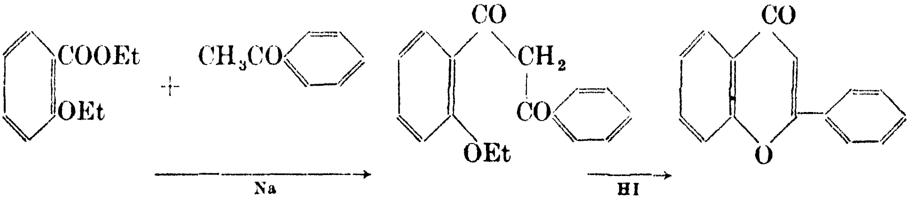
[1] Robinson *et al.*, *J.C.S.*, 1924, **125**, 188 ; 1925, **127**, 166 ; **1926**, 1968 ; 1931, 2665, 2701 ; 1932, 2299.

It will readily be seen that the structures are the ketone analogues of the anthocyanidin structures ; indeed, the relationship is so intimate that quercetin (346) has been reduced by magnesium and hydrochloric acid to cyanidin (347) :—



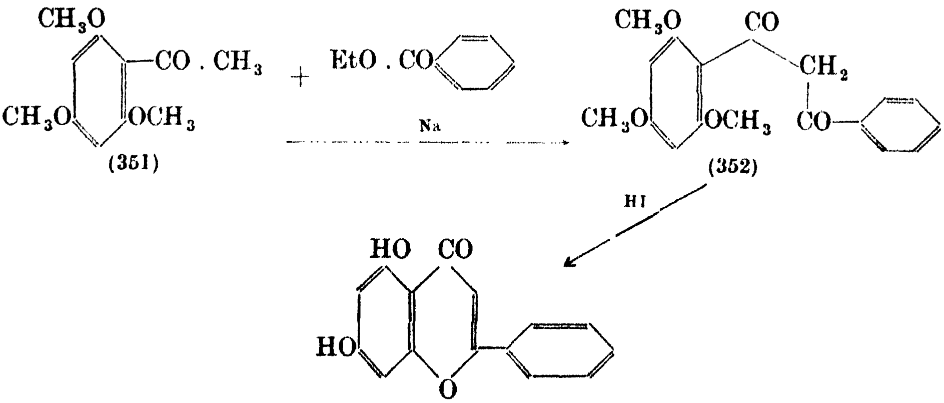
(346) (347)

Flavone occurs naturally as the ' meal ' or ' farina ' found as a water-and-insect-repellant on various Primula species (*P. pulverulenta*, *P. japonica*, *P. sikkimensis*, *P. auricula*, etc.). Müller [1] observed that on recrystallisation of this meal from benzene or ligroin tolerably pure flavone, m. 98°, is obtained. Various processes are available for the synthesis of flavone itself, the most satisfactory being, probably, that of Kostanecki and Tambor,[2] in which *o*-ethoxybenzoic ethyl ester is condensed with acetophenone (348) in the presence of sodium giving, thereby, *o*-ethoxydibenzoylmethane (349). The latter compound gives flavone (350) on boiling with hydriodic acid.



(348) (349) 350)

Some typical flavones are shown in Table XIII, and are mainly derived from 5, 7 dihydroxyflavone, or chrysin (353). This latter occurs in the early leaf-buds of various species of poplar, and accounts for the golden, shimmering appearance of these trees in early spring. The synthesis of chrysin is accomplished by condensing phloroacetophenone trimethyl ether (351) with ethyl



(353)

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[1] Müller, *Trans. C.S.*, 1915, **107**, 872.

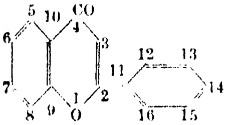
[2] Kostanecki and Tambor, *Ber.*, **1900**, **33**, 330.

benzoate in the presence of sodium when a substituted dibenzoyl methane (352) is obtained. The latter being boiled with hydriodic acid is demethylated completely, and the flavone ring formed by loss of the elements of water from the enolic form. This procedure is entirely analogous to the formation of flavone itself from the corresponding 2-hydroxydibenzoyl methane.

Similar syntheses have been arrived at for the majority of the aglycones illustrated in the second column of Table XIII.

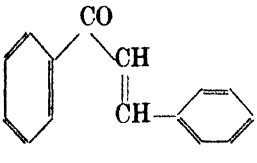
TABLE XIII

SOME FLAVONE PIGMENTS

Glucoside or related Structure	Aglycone	Combined with	Position of hydroxyls in  5 10 CO 4 6 3 12 13 11 14 7 1 2 8 9 O 16 15	Source
—	Chrysin	—	5, 7-	Poplar (*Populus* species)
Apiin	Apigenin	Apiose and glucose	5, 7, 14-	Parsley (*Petroselinum sativum*)
Anthemin	Apigenin	Glucose 2 mols.	5, 7, 14-	Chamomilte (*Anthemis nobilis*)
Acaciin	Apigenin	Rhamnose	5, 7, 14-	False Acacia (*Robinia* species)
Baicalin	Baicalein	Glucuronic acid	5, 6, 7-	Skullcap (*Scutellaria baicalensis*)
—	Lutelin	—	5, 7, 13, 14-	Dyers wold (*Reseda luteola*) Dyers broom (*Genista tinctoria*)
Galuteolin	Luteolin	Glucose	5, 17, 13, 14-	Goats-rue (*Galega officinalis*)
Diosmin	Diosmetin	2 mols. glucose + 1 mol. rhamnose	5, 7, 13, 14- 14 methyl	*Scrophularia nodosa*
Scutellarin	Scutellarein	Glucuronic acid	5, 6, 7, 14-	*Scutellaria* species
Lotusin	Lotoflavin	2 mols. glucose 1 mol. HCN	Tetrahydroxy	Lotus (*L. Arabica*)

FLAVANONE PIGMENTS

In this comparatively small group of pigments, the pyrone ring is fully saturated, so that they are virtually derivatives of 2, 3-dihydroflavone. This substance is related to chalkone (354), or benzylidene acetophenone. When



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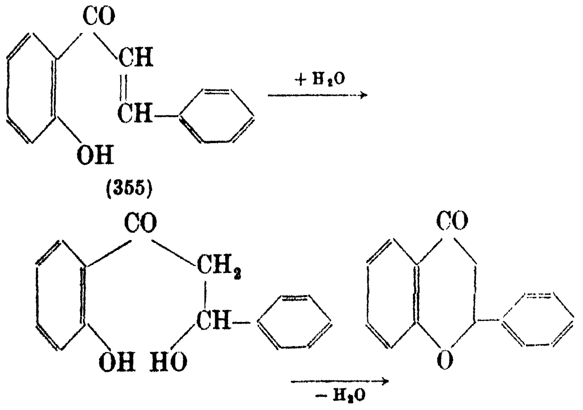
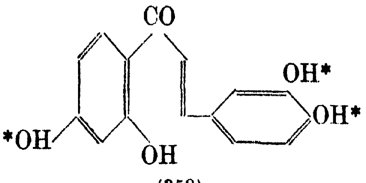


(355)

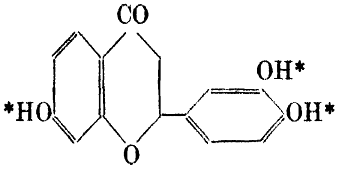
(356)

(357)

o-hydroxychalkone (355) is gently boiled with alcoholic sulphuric acid, flavanone is produced (357), presumably *via* the intermediate substance (356). Very often the chalkone and the corresponding flavanone (357) exist side by side in their natural source. Thus, the Dhak tree (*Butea frondosa*) has the chalkone, butein and its related flavanone, butin. These are both shown in (358) and (359).



(358)

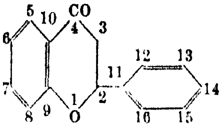
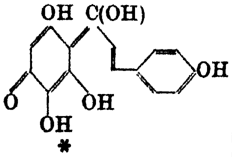


(359)

This hypothesis was confirmed by the work of Perkin and Hummel,[1] who were successful in synthesising the two trimethyl ethers of butein and butin (position of the etherifying groups is shown by * in the formulæ (358) and (359)). Other examples of flavanone pigments are shown in Table XIV.

TABLE XIV

SOME FLAVANONE PIGMENTS

Dyestuff or pigment	Aglycone	Sugar or other component	Position of hydroxyls in  5 10 CO 4 3 6 12 13 11 14 7 1 2 8 9 O 16 15	Source
Eriodictyol glycoside	Eriodictyol	?	5, 7, 13, 14	*Eriodictyon californicum*
Hesperidin	Hesperitin	7-Rhamnoglucoside	5, 7, 13, 14- (14-methyl)	The peel of citrus fruits, e.g. orange and lemon (*C. Aurantium* and *C. Limonum*)
Butin glucoside	Butin	7-glucoside	7, 13, 14-	Dhak tree (*Butea frondosa*)
Naringin	Naringenin	? Rhamnoglucose	5, 7, 14-	*Citrus decumana*
Sakuranin	Sakuranetin (7-monomethyl ether of naringenin)	Glucose	5, 7, 14- (7-methyl)	Japanese *prunus* species
Carthamin	A Chalkone 	Glucose (in position *)	—	Safflower or false saffron (*Carthamus tinctorius*)

THE FLAVONOLS

These differ from the flavones in having an additional hydroxyl group in the 3-position of the flavone ring; they form, therefore, a close link with many of the anthocyanidins. Flavonol itself (yellow needles, m. 168°) is obtained from flavanone by the action of amyl nitrite and hydrochloric acid on its alcoholic solution. An oximino derivative is formed (360) which, on boiling with dilute acids, yields flavonol (361).

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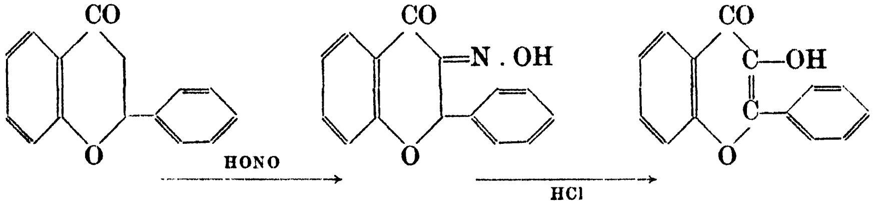
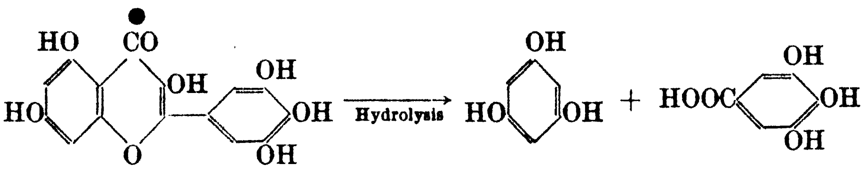
[1] Perkin and Hummel, *Trans. C.S.*, 1904, **85**, 1459.



(360) (361)

There are many examples of flavonol pigments found naturally, and their chemical identification depends on the fact that the pigment itself possesses the same number of hydroxyl groups as the products formed from it by hydrolysis. Thus, myricetin, for example, is a hexahydroxy compound giving gallic acid and phloroglucinol on hydrolysis :—



With flavone or flavanone pigments, the hydrolytic products have one hydroxyl more than the compound from which they were formed.

Some of the characteristic members of the flavonol group are shown in Table XV. The principal method of synthesis is *via* the flavanone, from the appropriate chalkone. In this way, kæmpferol (362) has been synthesised by the following sequence of reactions :—

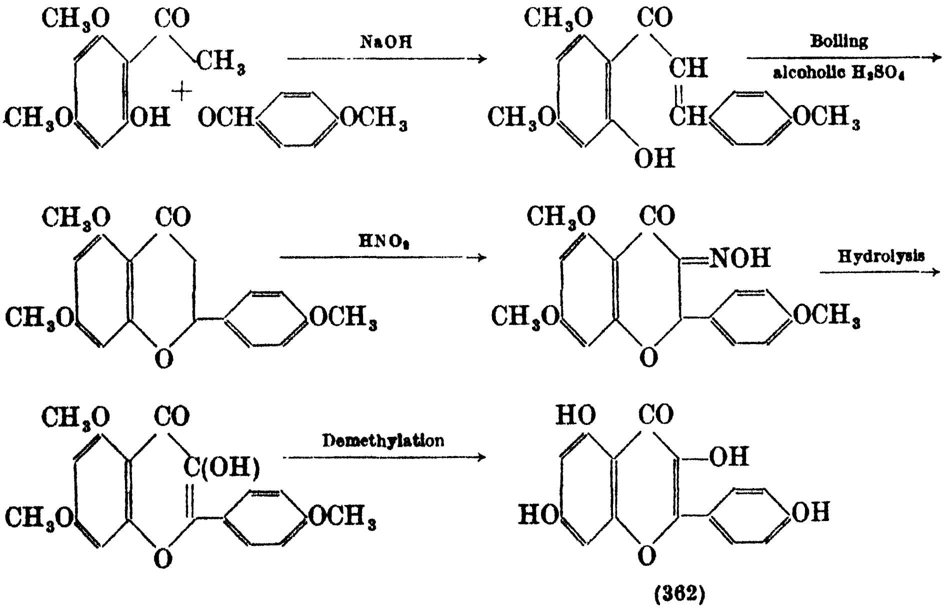


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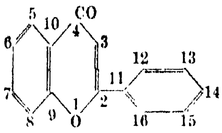
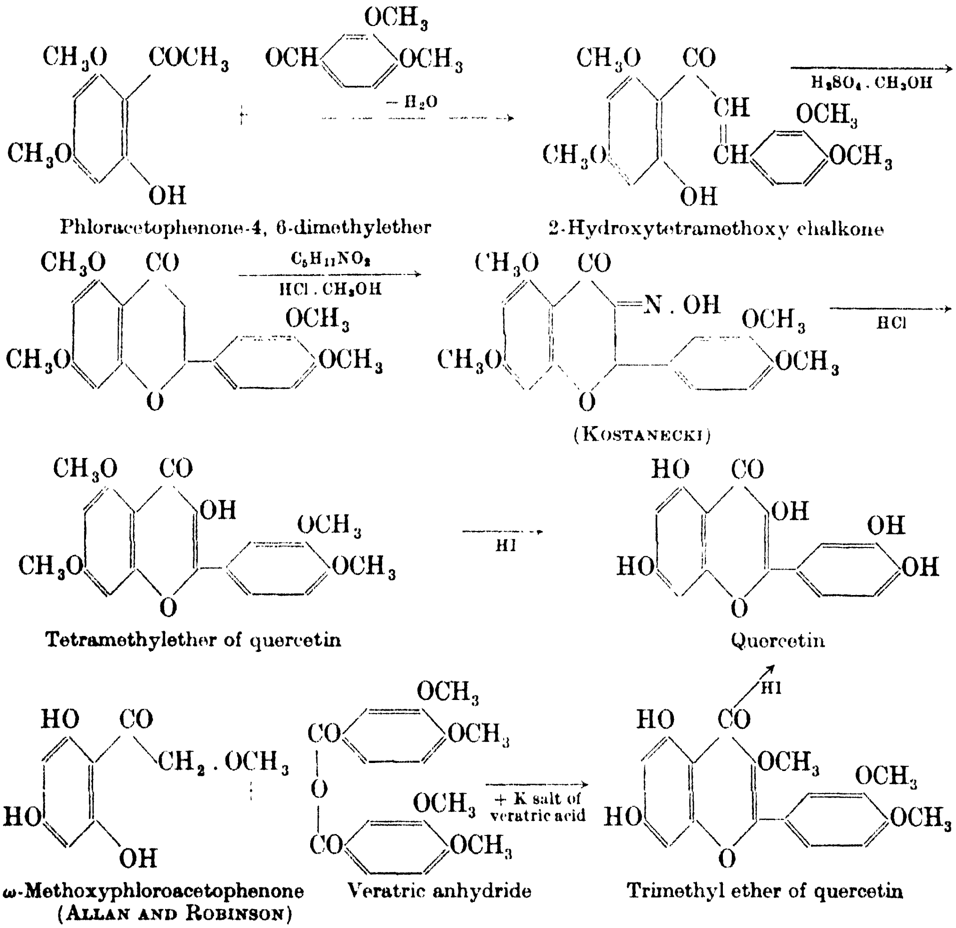
TABLE XV

SOME FLAVONOL PIGMENTS

Pigment	Aglycone	Sugar or other component	Hydroxyl groups in  5 10 CO 4 6 3 12 13 11 14 7 2 1 8 9 O 16 15	Source
Galanga glycoside	Galangin	3-Glucoside	3, 5, 7-	Galanga root (*Alpinia officinarum*)
Fustin	Fisetin	3-Rhamnoside	3, 7, 13, 14-	Young fustic (*Rhus cotinus*) Quetracho (*Q. colorado*)
Kæmpferide	Kæmpferol	14-Methyl ester	3, 5, 7, 14-	Galanga root.
Kæmpferitrin	Kæmpferol	3-Dirhamnoside	3, 5, 7, 14-	*Indigofera arrecta*
Kæmpferin	Kæmpferol	3-Diglucoside	3, 5, 7, 14-	'Senna' (*Cassia sp.*)
Robinin	Kæmpferol	The trisaccharide robinose (Glucose + 2 mols rhamnose)	3, 5, 7, 14-	False acacia (*Robinia pseudacacia*)
Datiscin	Datiscetin	Rutinose (glucose + rhamnose)	3, 5, 7, 12-	Bastard Hemp (*Datisca cannabina*)
Quercitrin	Quercetin	3-Rhamnoside	3, 5, 7, 13, 14-	Inner or 'quercitron' bark of Bark oak (*Q. tinctoria*)
iso-Quercitrin	Quercetin	3-Glucoside	3, 5, 7, 13, 14-	Cotton (*Gossypium*)
Quercimeritin	Quercetin	7-Glucoside	3, 5, 7, 13, 14-	Cotton (*Gossypium*)
Serotin	Quercetin	?-Glucoside	3, 5, 7, 13, 14-	Black Cherry (*Prunus serotina*)
Rutin	Quercetin	3-Rutinoside	3, 5, 7, 13, 14-	Rue (*Ruta graveolens*) *Capparis spinosa* *Sophora japonica*
Xanthorhamnin	Rhamnetin (Quercetin-7-monomethyl ether)	3-Rhamninoside (galactose + 2 mols rhamnose)	3, 5, 7, 13, 14- (7-methyl)	"Persian berries" (*Rhamnus sp.*)
—	*iso*-Rhamnetin (Quercetin-13-monomethyl ether	—	3, 5, 7, 13, 14- (13-methyl)	Wallflower (*Cheiranthus sp.*) Red clover (*Trifolium pratense*)
—	Rhamnazin (Quercetin-7, 13 dimethyl ether)	—	3, 5, 7, 13, 14- (7, 13-dimethyl)	Persian berries
—	Morin	—	3, 5, 7, 12, 14-	Old fustic (*Chlorophora tinctoria*). Osage orange (*Maclura aurantiaca*). 'Jakwood' (*Artocarpus integrifolia*)
Myricitrin	Myricetin	3-Rhamnoside	3, 5, 7, 13, 14, 15-	Box myrtle (*Myrica rubra*). Sicilian sumach (*Rhus coriaria*). Logwood leaves (*Hæmatoxylon campechianum*)
Gossypitrin	Gossypetin	?-Glucoside	3, 5, 8, 13, 14-	Cotton (*Gossypium*)
Quercitagitrin	Quercitagetin	?-Glucoside	3, 5, 6, 7, 13, 14-	African marigold (*Tagetes patula*)

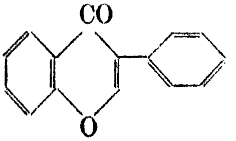
The main synthetic methods in this field are well illustrated by the synthesis of quercetin by Kostanecki,[1] and by Allan and Robinson.[2] The course of the reactions are sufficiently described by the formulæ set out below :—

Synthesis of Quercetin



THE *iso*-FLAVONE, DIHYDROPYRAN, AND XANTHONE FAMILY

In this section several small groups of natural pigments are brought together for convenience. The *iso*-flavones are derived from the structure (363), in



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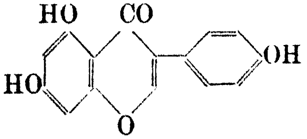

Genistein (364)

which the subsidiary phenyl group occupies the ' 3 '-position. The principal members of this group are set out in Table XVI, from which it is clear that they bear considerable resemblance to the normal flavones. Synthesis of

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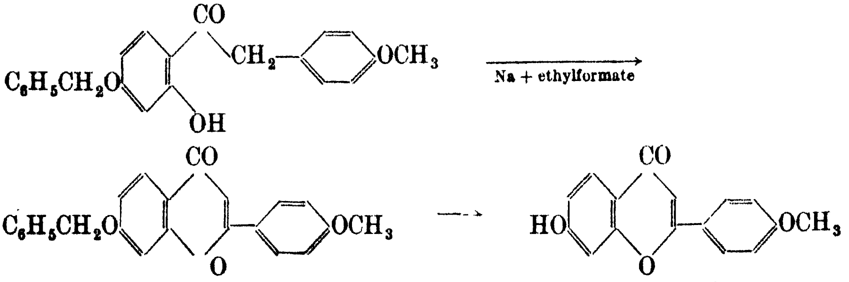
[1] Kostanecki *et al.*, *Ber.*, 1904, **37**, 1402.

[2] Allan and Robinson, *J.C.S.*, 1924, **125**, 2192 ; 1926, 2334.

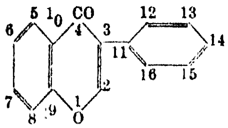
iso-flavones is effected by ring closure of derivatives of phenyl benzyl ketone, as shown below with formonetin :—



Formonetin

TABLE XVI

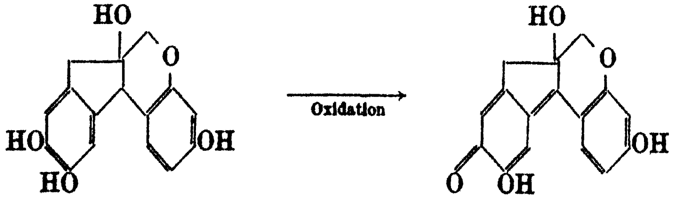
SOME *iso*-FLAVONES

Dyestuff	Aglycone	Sugar or other component	Position of hydroxyls in 	Source
Genistin	Genistein	7-Glucoside	5, 7, 14	Dyers Broom (*Genista tinctoria*); also contains genistein. From soya bean (*S. hispida*)
Prunetin	Genistein	14-Methyl ether	5, 7, 14 (14-methyl)	*Prunus sp.*
ψ-Baptisin	*ψ*-Baptigenin	7-Rhamnoglucoside	7, 13, 14 (13-14 methylene-dioxy)	*Baptisia tinctoria*
?	Tectorigenin	Glucoside	5, 6, 7, 14 (6-methyl)	
Iridin	Irigenin	7-Glucoside	5, 6, 7, 13, 14, 15 (6, 13, 14 trimethyl)	Iris (*I. florentina, germanica* and *pallida*)
Daidzin	Daidzein	7-Glucoside	7, 14	Soya

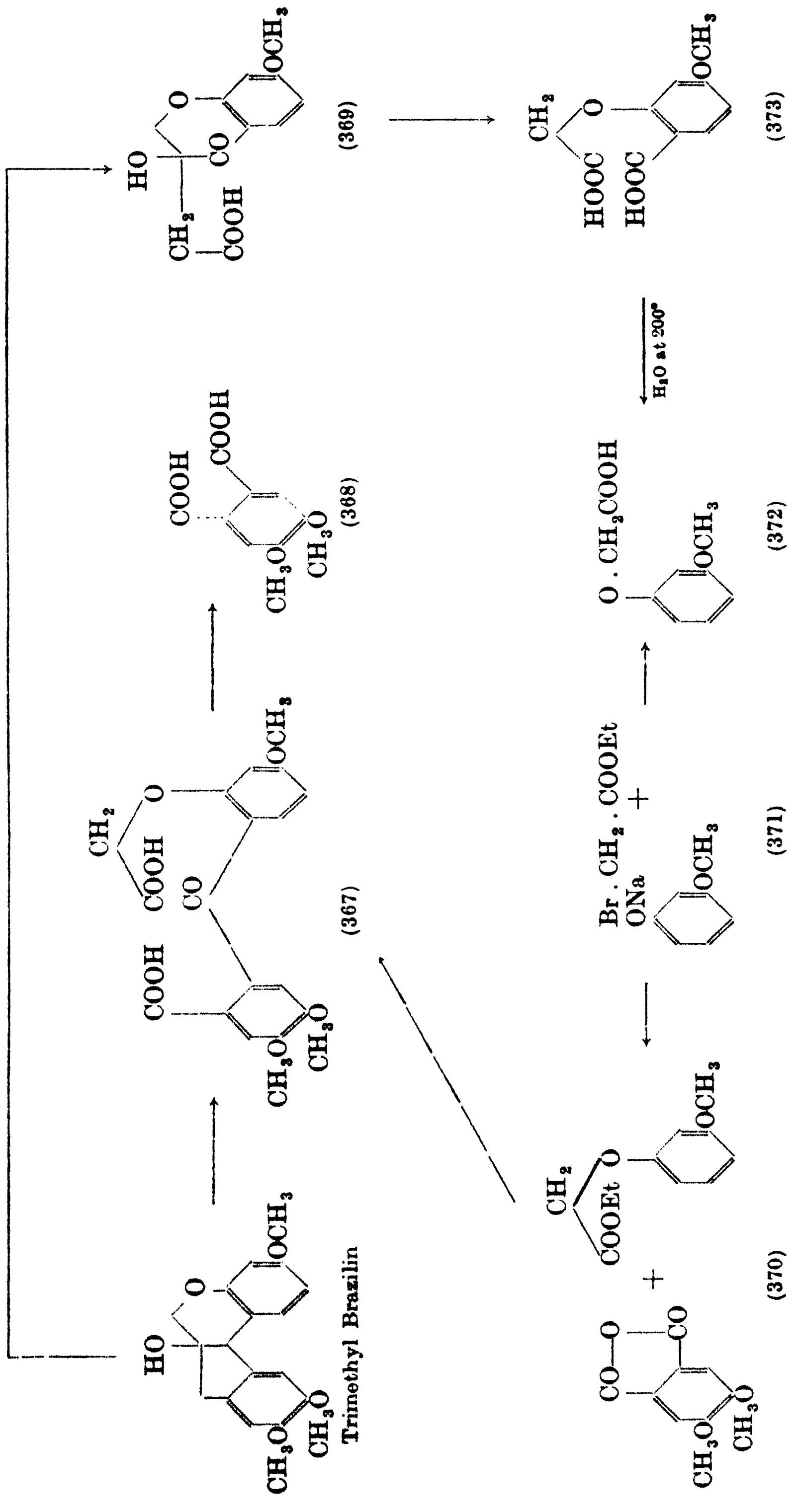
The dyewoods, brazil-wood and logwood were used quite early in the history of dyeing to obtain purple and black shades, and are, to a limited extent, still used for this purpose. The brazil-woods, of which there are several, are varieties of *Cæsalpina* ; the main types are

Cæsalpina crista.—Pernambuco wood, from Jamaica and Brazil.
Cæsalpina braziliensis.—Brazil wood (true), from Brazil.
Cæsalpina echinata.—Peach wood, Central and Northern S. America.
Cæsalpina sappan.—Sappan wood, Asia and the Philippines.

The active principle of these woods is brazilin (365), which is oxidised to a deep red quinonoid dye brazilein (366), which gives the dark mordanted shades.



Brazilin (365) **Brazilein (366)**


Trimethyl Brazilin
(367)
(368)
(369)
(370)
(371)
(372)
(373)
H₂O at 200°

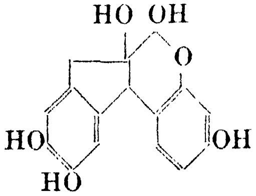
Crystalline brazilin was obtained by Chevreul[1] as long ago as 1808. The correct empirical formula was worked out by Liebermann and Burg in 1883. The constitution of brazilin (365) and brazilein was largely established by the researches of Perkin and Robinson,[2] and depends to a considerable extent on the breakdown of trimethylbrazilin.

Briefly, the salient points in this degradation are as follows. Trimethyl brazilin on oxidation yields

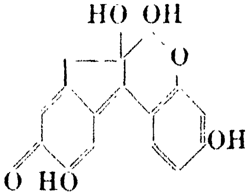
(1) *m*-Hemipinic acid (368).
(2) 2-Carboxy-5-methoxyphenoxyacetic acid (372).
(3) Brazilic acid (369).
(4) Brazilinic acid (367).

Brazilinic acid (367) has been synthesised by the action of hemipinic anhydride on 3-methoxyphenoxyacetic ester (370), the corresponding acid being also obtained both by synthesis (371) and by the decarboxylation of 2-carboxy-5-methoxy-phenoxyacetic acid (373).

Logwood, or Campeachy wood, is from the tree *Hæmatoxylon campechianum* (Linn.), and contains the crystalline compound hæmatoxylin; this, like brazilin, is easily oxidised, and when so treated gives the quinonoid dye hæmatein (not to be confused with the hæmatin of blood). Hæmatoxylin and hæmatein are hydroxybrazilin (374) and hydroxybrazilein (375).

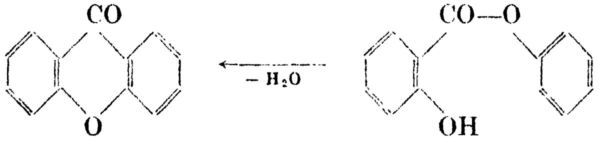


(374)



(375)

Xanthone pigments are derived from the structure (376), xanthone itself,



(376) (377)

which was first prepared by Kolbe and Lautermann[3] by the action of phosphorus oxychloride on sodium salicylate. It is now prepared by the dehydration of salol (phenyl salicylate) (377) by slow distillation. Xanthone forms long needles, m. 174°, soluble with a blue fluorescence in sulphuric acid. It has the following chemical characteristics :—

(1) It is sufficient of an oxonium compound to give a hydrobromide, a stannichloride, and a perchlorate.
(2) Hydriodic acid or zinc distillation reduce it to xanthene (378).
(3) Alkali fusion gives 2, 2′-dihydroxybenzophenone (379).
(4) Zinc and alkali reduce xanthone to xanthydrol (380), a valuable reagent for the estimation of urea.
(5) With zinc and acetic acid a dixanthylene derivative is obtained (381).

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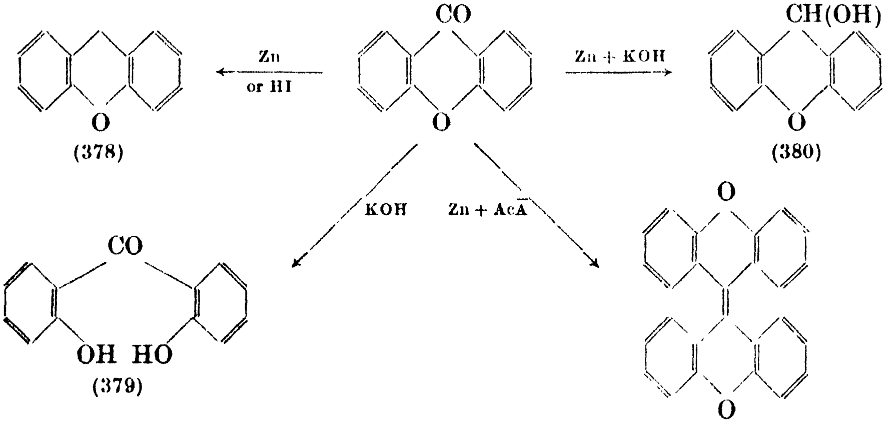
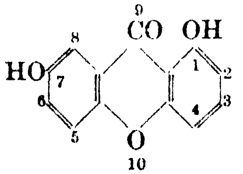
[1] Chevreul, *Ann. Chim. Phys.*, 1808, **[1]**, **66**, 225.
[2] Perkin and Robinson, *J.C.S.*, 1908, **93**, 496.
[3] Kolbe and Lautermann, *Ann.*, 1860, **115**, 197.

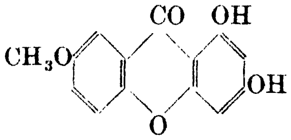


(378) (380) (379) (381)

Cows fed on mango leaves (*Mangifera indica*) have a deep yellow urine which, if warmed, deposits a yellow pigment. The insoluble pigment is made into balls and constituted, at one time, the 'Indian Yellow' of commerce. It is largely euxanthic acid, the 7-glucuronic acid derivative of euxanthone (1, 7-dihydroxy xanthone) (382), and is present as the calcium or magnesium salt.

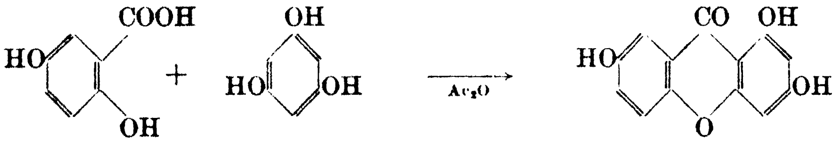


(382)



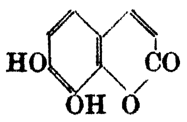
(383)

Gentisin, the yellow pigment from *Gentiana lutea*, is the 9-methyl ether of 1, 3, 7-trihydroxyxanthone (383) called, for inconvenience, gentisein. These two colouring matters are easily synthesised by boiling together resorcinol or phloroglucinol with 2, 5-dihydroxy benzoic acid, in acetic anhydride solution, e.g. :—

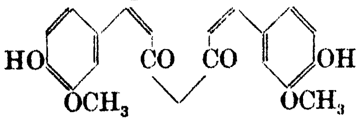


Daphnetin.—It is hardly surprising that some of the α-pyrones show colour, and that the polyhydroxycoumarins are mordant dyes. One which has attracted some attention from an academic standpoint is daphnetin, 7, 8-dihydroxycoumarin (384), the 7-glucoside of which is the active principle, daphnin, of various *Daphne* species, including *D. mezereon.*

Turmeric, the underground rhizome of *Curcuma longa* contains a powerful yellow pigment, curcumin (385) which Ciamician and Silber, as far back as 1897, regarded as a dicinnamoylmethane compound. It was subsequently



(384)



(385)

shown to be a dimethoxydihydroxydicinnamoyl methane (385), and was synthesised by Lampe.[1]

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[1] Lampe, *Ber.*, 1918, **51**, 1347.

APPENDIX III

PHOTOGRAPHIC DEVELOPERS

Many organic substances are capable of acting as photographic developers, and their manufacture occupies a significant place in the industry of chemical synthesis. The latent image on a photographic film or plate is produced by the photochemical decomposition of silver halide ; early investigators thought that a subhalide was formed, but later investigators incline to the view that the effect is due to the incidence of light engendering a disturbance in the silver/halogen lattice, by which some halogen ions escape, leaving the lattice relatively richer in silver. Thus, although the silver halide has not changed visibly, it is, after exposure, permeated with silver ions, the concentration of which will vary according to the intensity and length of exposure.

Many organic compounds, mainly phenols and amines, have the power to 'develop' or render visible the silver-ion pattern of the latent image. Thus, pyrogallol, one of the earliest developers, was first used in 1872 ; Abney, in 1880, introduced hydroquinone, and a few years later Andersen drew attention to the developer properties of *p*-phenylene diamine, and of sodium aminonaphthol sulphonate. The whole field was carefully investigated during the last two decades of the nineteenth century by the Lumières,[1] and from the more academic aspects, by Homolka. Two very important conclusions were reached during these researches : (1) that there is a fundamental difference between 'development' and mere reduction ; many phenols and amines which are excellent reducing agents for silver salts are without the power of rendering the latent image visible ; and (2) that *ortho*- and *para*-substituted compounds show developer properties whilst *meta*-substituted compounds do not.

The former observation, largely due to the work of the Lumières, appears to be related to the rate of deposition of the added silver. It is essential for the correct development of the latent image, that the amount of metallic silver deposited shall be strictly proportional to the lattice-ion-disturbance. With many organic reducing agents the tendency is to create a 'snowball' effect, where the first particles of silver formed engender the formation of further metallic silver with the result that the plate is blackened all over indiscriminately. This tendency is restrained in many ways : by incorporating sulphur compounds, such as thiourea, into the emulsion ; by using bromides in the developer ; and by using such developing substances as will cause proportionate deposition. In this connexion, it may be remarked that the 'unit' of the photographic image is the silver halide grain, silver being uniformly deposited throughout each individual grain to the degree warranted by the disturbance of its space-lattice, and to a degree proportional to the intensity of the original exposure. Thus, as far as may be practical, attempts are made to obtain as fine-grain an emulsion as possible, since the absence of variations in density throughout the individual grain makes this the controlling factor in the ultimate resolution of the image.

Homolka drew attention to the fact that the observations of the Lumières (that true developing properties were present in *o*- and *p*-substituted compounds, and not in *m*-substituted substances) are only true when the members of the latter group are capable of keto/enol tautomerism. Thus, phloroglucinol,

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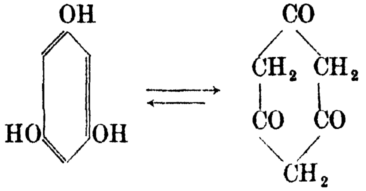
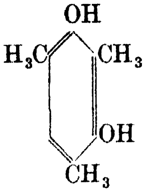
[1] A. and L. Lumière published their results in the *Bull. Soc. franc. photog.* (between 1891 and 1914), which is not easily available in this country. A summary of their work will be found in the reports of the 7th and 8th Congresses of Industrial Chemistry (*Chimie Industrie Congrès chim. ind.*), 1927 and 1928.

m-aminophenol, resorcinol, and many of their analogues which can show tautomerism as in (386), are useless as developers; on the other hand,



(386)



(387)

'mesoresorcin' (dihydroxymesitylene) (387), in which keto-enol tantomerism is precluded by the presence of the methyl groups, is an excellent developer.

The main substances used as photographic developers are listed in Table XVII.

TABLE XVII

SOME PHOTOGRAPHIC DEVELOPERS

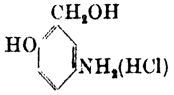
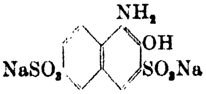
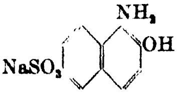
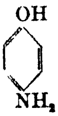
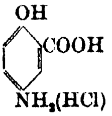
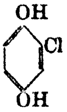
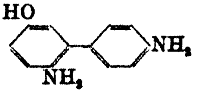
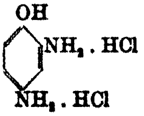
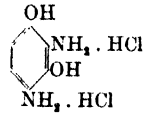
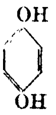
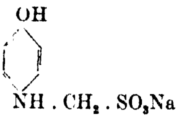
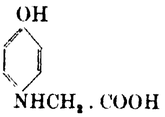
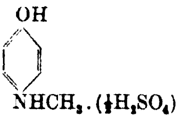
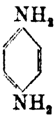
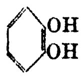
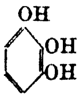
Name	Formula	General properties
3-Amino-6-hydroxybenzyl alcohol (hydrochloride) Edinol		Yellowish crystalline powder easily soluble in water
1-Amino-2-naphthol-3, 6-disulphonic acid (Na salt) Diogenal (Diogene)		Colourless needles, decomposing without melting on heating. Easily soluble in water
1-Amino-2-naphthol-6-sulphonic acid (Na salt) Iconogen (Eikonogen)		A dihydrate crystallising in rhombohedra. It is easily soluble in water
4-Aminophenol		Both the base m. 184°, and the hydrochloride are used as developers. Both are soluble in water, but the base is sparingly so in the cold
5-Aminosalicylic acid hydrochloride Neol		Crystallises in long needles which can be sublimed. Not very soluble in water, but readily soluble in alkaline sulphite solution
Chlorohydroquinone Adurol		Forms needles, m. 104°, easily soluble in water, alcohol and ether. With metol base, it combines to form chloranol
Diaminohydroxydiphenyl Diphenal		An 'acid' developer; forms long needles, m. 148°
2, 4-Diaminophenol dihydrochloride Amidol		Colourless needles, easily soluble in water. A widely-used developer

TABLE XVII (*continued*)

Name	Formula	General properties
2, 4-Diamino resorcin dihydrochloride		An improvement on Amidol, but more expensive
Hydroquinone		Long hexagonal prisms. One of the most widely used developers; often used in combination with *p*-phenylene diamine as Hydramine
4-Hydroxyphenylamino methane sulphonic acid (Na salt) EUREKIN		Needles, easily soluble in water
p-Hydroxyphenylglycine GLYCINE		Plates; not very soluble in water, but sulphites and alkalies are able to form easily soluble compounds
p-Methylamino phenol sulphate METOL		Needles, easily soluble in water. A favourite developer; the base forms a double compound with hydroquinone, often known as 'M-Q'
p-Phenylene diamine		Triclinic prisms; m. 117° b. 267°. Very liable to cause dermatitis in use
Pyrocatechol		Easily soluble in water; has only recently become available technically, and shows some advantages over pyrogallol
Pyrogallol		Needles in 126°. A well-tried and 'contrasty' developer

APPENDIX IV

FERMENTATION AND ENZYME ACTION

The study of fermentations and of enzyme action constitutes a definite and important section of biochemistry, and has been the subject of so much research, that in this Appendix only a few aspects can be touched upon, and these only in brief.

Fermentations have been known from time immemorial; the conversion of saccharine liquids to alcoholic liquors (grape-juice to wine or barley-wort to beer), the formation of vinegar, and the souring of milk are all processes known to the ancients, and used productively, but these users had no conception of the precise causes underlying the changes. Knowledge of fermentation was considerably advanced when Pasteur showed that in vinous fermentation, the inoculation is caused by air-borne yeast cells, and that chance inoculation by unsuitable (' wild ') yeasts or other organisms might result in spoiling the wine. This brought the rationale of vinous fermentation into line with the then existing knowledge on the yeast fermentation of sugar and cereal worts, with the production of alcohol.

TABLE XVIII

SOME COMMON ENZYMES

No.	Name of enzyme	Enzymes resembling or identical with—	Substrate	Products	Source
1	Amygdalase		Amygdalin	Mandelonitrile glucoside + glucose	Almond seeds
2	Amylase	Diastase	Starch and dextrins	Maltose	Many plants
3	Arginase		Arginine	Ornithine + urea	Vetch sprouts
4	Carboxylase		α-Ketonic acids	Aldehydes + CO_2	Yeast; and some roots
5	Catalase		Hydrogen peroxide	Water and O_2	All higher plants
6	Cellulase	Cytase	Cellulose Hemicellulose	Cellobiose Reducing sugars	Seeds
7	Chlorophyllase		Chlorophyll	Phytol + chlorophyllide	Green leaves
8	Citric oxidase		Citric acid	A mixture + CO_2	Cucumber seeds
9	Deaminase		Amino-acids	Hydroxy-acids + NH_3	Liver; bacterial cells; Plants
10	Erepsin	Peptidase, Asparginase	Peptones and peptides	Amino acids	Intestinal tract Plants
11	α-Glucosidase	Maltase	Amides α-Glucosides (both heterosides and holosides)	Amino acids + NH_3 Glucose + hexoses or hydroxy compounds	Germinating barley Leaves; cereal grains
12	β-Glucosidase	Primase Emulsin	β-Glucosides	Ditto	Cherry and allied sp. leaves
13	Indophenol oxidase		Cytochromes	Oxidised cytochromes	Yeast
14	Indemulsin		Indican	Glucose + indoxyl	*Indigofera sp.*
15	Invertase	Sucrase	Sucrose	Invert sugar	Many plants; yeast
16	Inulase		Inulin	Fructose	Dahlias and artichokes
17	Lipase		Fats	Fatty acids + glycerol	Animal tissues; liver; Seeds
18	Oxalic oxidase		Oxalic acid	CO_2 + H_2O	Orange seeds; rhubarb
19	Oxido-reductase	Reductase	Nitrate	Nitrite	Bacteria (meat pickling) Plants
20	Oxygenase		Dihydroxy aryl compounds	Quinones	Most higher plants
21	Oxynitrilase	Emulsin	Mandelonitrile	Benzaldehyde + HCN	Cherry and laurel leaves
22	Pectase		Pectin	Pectic acid + methanol	Clover
23	Pectinase		Pectin	Aldohexoses	Sprouting cereals
24	Pepsin		Proteins	Proteoses and peptones	Stomach
25	Peroxidase		Hydrogen and organic peroxides	Water + oxygen	Plants
26	Phosphatase	Phytase	Phytin	H_3PO_4 + inositol	Seeds
27	Proteases	Papain, Bromelin (? mixtures of erepsin + pepsin)	Proteins	Proteoses and amino-acids	Fruits, especially Pawpaw and pineapple; animal tissues
27a	Rennin		Caseinogen	Casein	Calf Stomach

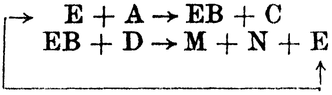
TABLE XVIII (*continued*)

No.	Name of enzyme	Enzymes resembling or identical with—	Substrate	Products	Source
28	Sinigrinase	Myrosin	Sinigrin	Allyl thiocarbimide + glucose + $KHSO_4$	Crucifers
29	Thrombase		Prothrombin		Blood
30	Trypsin		Proteins	Polypeptides and Amino-acids	Pancreas
31	Urease		Urea	Cyanic acid + NH_3	*Micrococcus ureæ* Soya bean
32	Xanthine oxidase		Xanthine	Uric acid	Lupin seeds
33	Zymase	(A mixture)	Hexoses	Alcohol + CO_2	Fruits and yeast

It was only natural that chemists of subsequent generations should enquire more closely into the precise mechanism of fermentation. Many chemists regarded fermentation as indissolubly bound up with the life processes of the fermenting organism, but Liebig, who made a close study of the matter, opposed this view, although at that time his views of the matter were not generally accepted. It remained for Buchner, in 1897, to show that the active principle of fermentation could be liberated from yeast cells by grinding them with sharp sand, and that a filtered extract could be obtained which would effect the conversion of glucose to alcohol in the same manner as the cell itself. It was thus first demonstrated that the ferment, or 'enzyme', can exist and discharge its especial duty apart from the living organism. Following this important advance, many enzymes have been prepared, many in sufficiently pure state to show crystalline structure (e.g. pepsin, trypsin and rennin). Thus it can now be taken as a starting point in the chemical study of enzymes and fermentation, that enzymes are chemical individuals of considerable complexity which are capable of acting on organic substances in a manner similiar to the catalysts, familiar in inorganic chemistry. For convenience a number of the more common enzymes and their properties are summarised in Table XVIII.

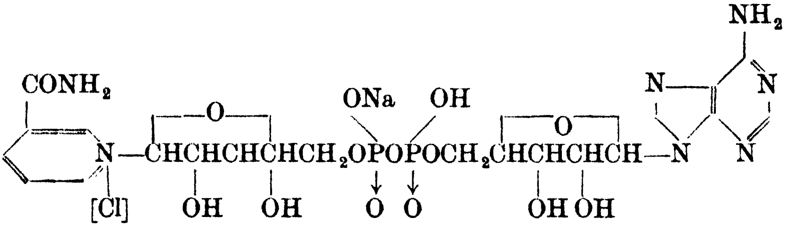
This list (Table XVIII) makes no pretence of being exhaustive, since many other enzymes are known. Little is known of their chemistry considered from a structural standpoint; and having regard to the great difficulties of obtaining them in a pure state, it is not unlikely that some enzymes now regarded as different will be found ultimately to be impure forms of the same substance, and that others now regarded as homogeneous will be found to be mixtures. In this connexion it must be remarked that the same enzyme from different sources may appear different owing to the preponderance of secondary material with which it is mixed; indeed, the differences of optimum pH at which they work may be conditioned, not by the enzyme, but by the impurities with which the preparation is mixed. Thus the three 'enzymes' (or varieties of enzyme) of the lipase group obtained from castor seeds, *Carica papaya* and aspergillus have optimum pH values for the hydrolysis of tributyrin at 5, 6 and 8·6 respectively. This does not, however, prove that they are different, but that the effect of the admixed impurities requires a different pH for suppression according to their nature and that of the source from which they are derived.

The fermentation of sugars to alcohol affords an example of enzyme action illustrating the complexity of the stages involved. The enzyme involved, zymase, has been shown to be a mixture, and to contain a number of individual compounds, or enzymes, each with a specific purpose, together with a number of essential ancillary substances. Of these, cozymase is interesting on account of the fact that its structure has been revealed; similarly cocarboxylase is known to be the pyrophosphoric ester of vitamin B_1. The formula of cozymase is given in (388). Thus, it appears that the enzymes are all, most probably, substances of definite, albeit complex, structure, and that their activity may be regarded as the regenerative E in the cycle :—



$$E + A \rightarrow EB + C$$
$$EB + D \rightarrow M + N + E$$

The scheme shown on page 374 indicates the complexity of the processes of alcoholic fermentation, and even so, has been simplified by the omission of any reference to the phosphoric acid cycle, which involves the formation and decomposition of adenine triphosphate. A glance at this scheme will immediately indicate the large part played by phosphoric acid and its esters in the fermentation of sugars.

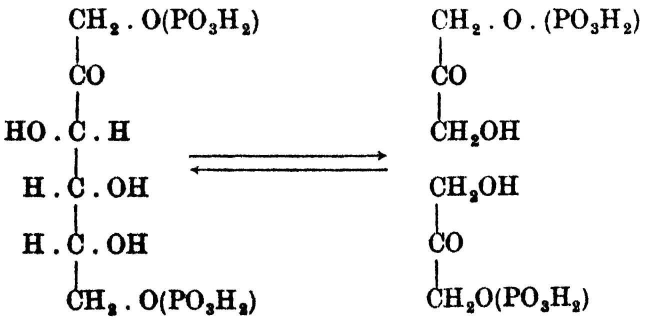


(388) Cozymase

In the first stage, the formation of a hexosediphosphate molecule is of paramount importance ; this essential step, the importance of which was demonstrated by Harden and Young, gives the key to much that follows. For more easy consideration the discussion of the fermentation is divided into *Stages*. It must, however, be premised that the reactions described are often only the principal changes to be associated with these stages, and that many side-reactions take place. The scheme set out on page 374 is almost identical with that of Meyerhoff and Kiessling.[1]

Stage A.—The formation of the hexose diphosphate appears to be associated with the enolisation of the sugar giving the 1, 6-diphosphoric ester of fructofuranose. This in itself is a complex process, and mannose 6-phosphate has been found in small quantity accompanying the fructofuranose ester. Willstätter goes so far as to suggest that the formation of hexose diphosphate is completely indirect and takes place with the intermediate formation of glycogen ; there is, however, little evidence for this, and the viewpoint was taken up before the true significance of the phosphoric esters was realised. It is generally held that the true mechanism of hexose diphosphate formation is through the isomerisation and enolisation of glucose.

Stage B.—Meyerhoff and his co-workers were able to demonstrate that in



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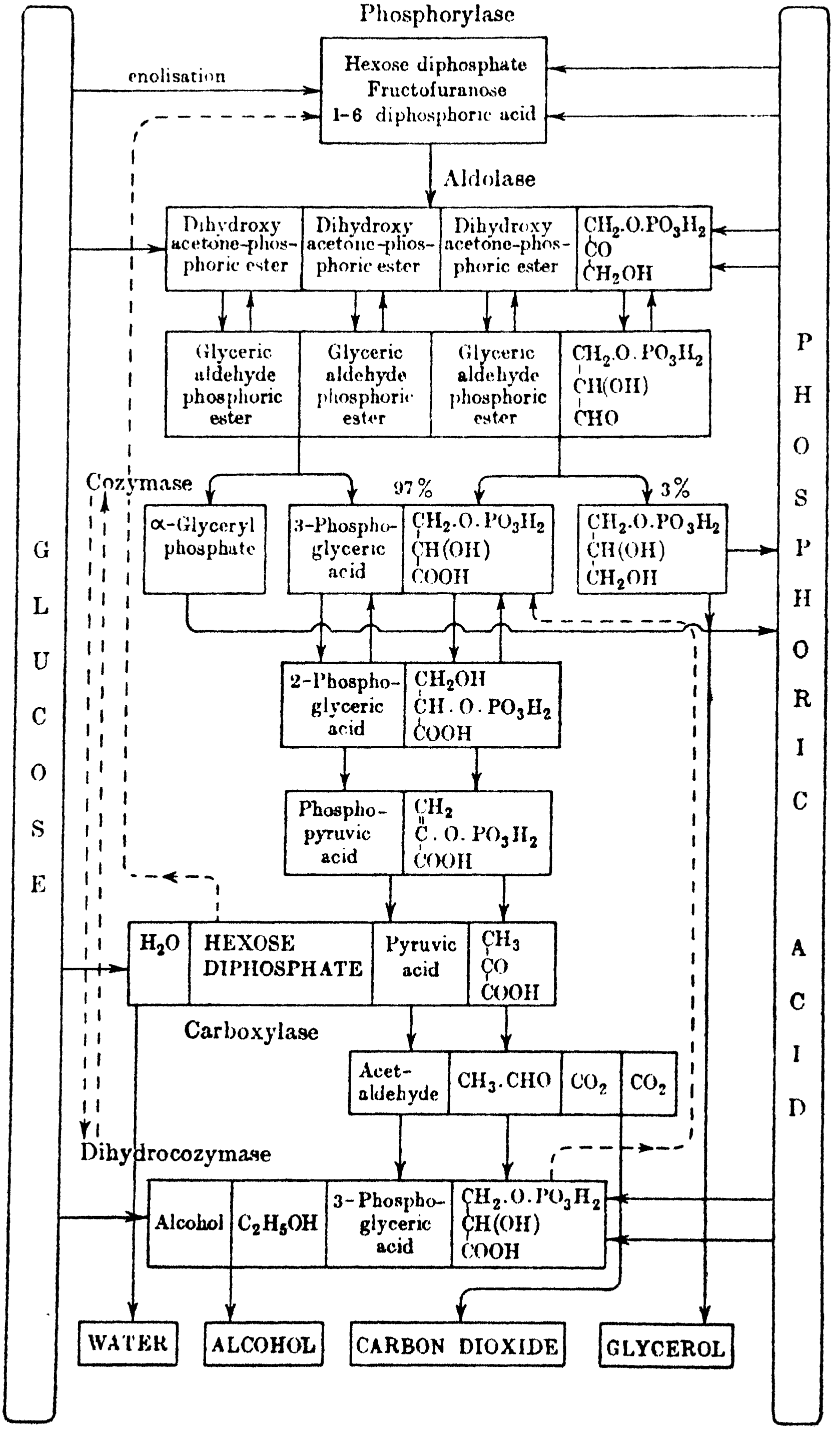
[1] Meyerhoff and Kiessling, *Biochem. Z.*, 1935, **281**, 249, and **283**, 83.

Diagrammatic Scheme of Glucose Fermentation



contact with yeast enzymes, fructo-furanose-1, 6-diphosphate is very readily converted to dihydroxyacetone phosphoric ester. The procedure shown at foot of page 373 is reversible, and although a structural dismutation, is capable of attaining true equilibrium in the presence of yeast enzymes. An enzyme, aldolase, is responsible for this disproportionating reaction.

Stage C.—The dihydroxy acetone phosphoric ester described in the previous stage passes quite readily into the isomeric glyceric aldehyde phosphoric ester, and this is converted by cozymase to a mixture of 2- and 3-phosphoglyceric acid (mutually intraconvertible) and α-glycerol phosphoric ester. At the same time the cozymase is reduced to dihydrocozymase. The diagram (p. 374) does not indicate that the main reaction is the conversion of aldehyde to acid and that formation of α-glycerol phosphoric ester is a side reaction, and does not withdraw more than a few per cent. of material from the main reaction unless some reagent, such as bisulphite, is present to stop the formation of ethanol from acetaldehyde, under which circumstance glyceryl and phosphoric ester is formed by utilisation of the hydrogen of dihydrocozymase. The phosphoric radicle is ultimately split off from the glycerol, which is found to an extent of about 3 per cent. in the wash from a normal fermentation, although with sulphites present the glycerol content can be increased to 36-37 per cent. This constitutes a well-known and industrially used method of manufacturing glycerol.

Stage D.—The main product of the previous stage, 2-phosphoglyceric acid, is found to lose the elements of water, giving the phosphoric ester of the enolic form of pyruvic acid. It is not yet clear as to whether this action is purely chemical, but it is followed by an indubitable enzyme action, namely the transference by an enzyme of the phosphoric residue to glucose with formation of hexose diphosphate and liberation of pyruvic acid itself. The hexose diphosphate thus carries the phosphoric acid back in the form of a regenerative cycle.

Stage E.—The decarboxylation of pyruvic acid to acetaldehyde and carbon dioxide is a simple process brought about by carboxylase.

Stage F.—The reduction of acetaldehyde to alcohol is complex; the presence of phosphoric acid, glucose and hexosediphosphate is necessary in addition to the aldehyde, and the net result of the reduction is that the hydrogen of dihydrocozymase is transferred to aldehyde, two molecules of 3-phosphoglyceric acid are formed and cozymase is liberated; both the latter are, therefore, part of a cycle of operations (indicated by a broken line in the scheme on page 374). There is much evidence to indicate that a labile hexose monophosphate is involved in this stage of the process, but even if present its significance is not clear.

By these complex stages glucose becomes converted to alcohol—usually by the actual growth of yeast in the solution; the maximum concentration of alcohol which is produced is about 18 per cent.

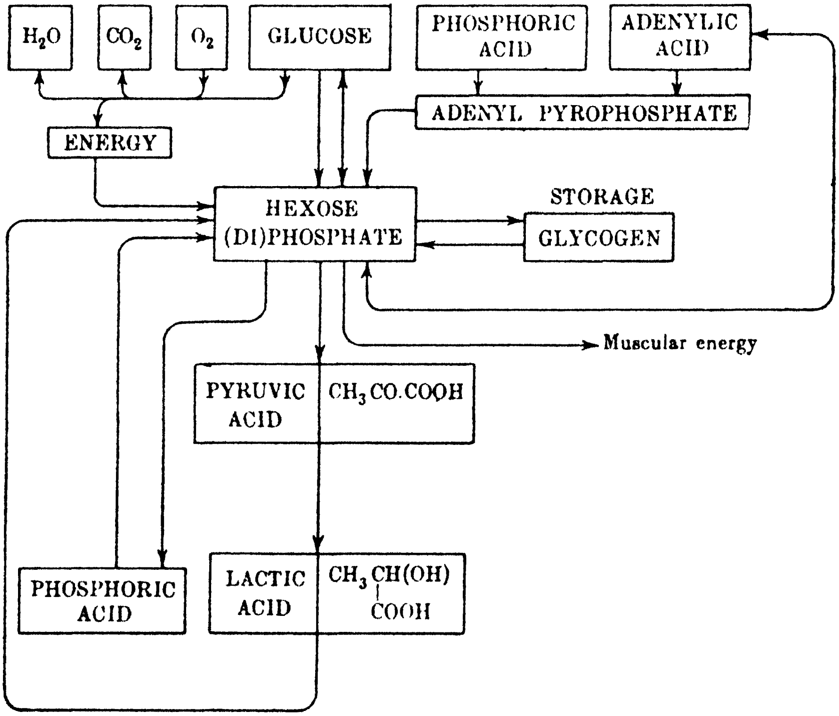
Many other enzyme actions are known, but only a few have received the detailed study necessary for a proper knowledge of the chemistry of their intermediate stages. Similar, in some ways, to the processes of alcoholic fermentation, are the processes of muscle metabolism, indicated in outline in the diagrammatic scheme on page 376. The central point in animal carbohydrate metabolism is glucose, and this sugar may be either built up in storage depots as the starch glycogen, or " burnt " with the release of energy. It is the latter process which has been the subject of much investigation; essential steps in the cycle is the reaction of glucose with adenyl pyrophosphate to give a hexosediphosphate and adenylic acid, and the effect of adenosinetriphosphatase on the myosin fibres of muscle tissue.[1] It is clear that if work is done by muscular contraction a corresponding quantity of energy must be transformed chemically; this is liberated by the oxidation of the hexose-phosphate-phosphatase system by the oxygen of the blood stream; as shown in the diagram below, the first recognisable breakdown product is pyruvic acid, but lactic acid is one of the resting points in the degradation. There is, however, a partial re-synthesis of lactic and phosphoric acids to give more hexose phosphate glucose and part of the lactic acid furnishes the necessary energy for this purpose by complete oxidation to carbon dioxide and water.

---

[1] For a detailed survey of the relation of myosin and adenosine triphosphatase see D. M. Needham, *Biochem. J.*, 1942, **36**, 113 and K. Bailey, *ibid.*, p. 121.

Thus the contraction of muscle fibre is associated with the conversion of hexose mono- or di-phosphate to lactic acid; recovery of muscle tissue is likewise associated with the reverse process; since the latter process is slower than the former, there will arise a deficit in hexose diphosphate and a surplus of lactic acid after persistent repetitive muscular effort, leading to the condition of fatigue.

Diagram of Muscle-Action



A limited application of enzyme processes is made in the large-scale production of certain organic chemicals. Some typical examples are :—

1. *Itaconic acid.*—A 20 per cent. solution of corn-syrup is inoculated with *Aspergillus terreus.* As the organism is of surface growth, the fermentation is carried out in shallow glass-lined pans. After 10-12 days the filtered liquor is concentrated and yields one pound of itaconic acid for each four pounds of sugar consumed.
2. *Citric acid,* although of natural occurrence in the juice of lemon and pineapple, is produced in considerable quantities by the fermentation of glucose by *Citromyces. Gluconic acid* can also be prepared industrially by fermentation.

3. *l-Sorbose* is obtained industrially from the fermentation of sorbitol by the sorbose bacterium.
4. *Penicillin* is obtained as a product of the fermentative life-cycle of *Penicillium notatum* (see Vol. II, ' Medicinal Chemicals ').
5. *Butyl alcohol* and *acetone* are obtained by the fermentation of maize mash.
6. *Butyric and lactic acids* can both be obtained in industrial bulk by the action of the appropriate organism on media rich in lactose (e.g. whey).

In general, however, it is not possible to advance detailed chemical explanations of the stages involved.

CHAPTER VI

THE ALDEHYDES AND KETONES

> " HYDRIDE OF BENZOYL, . . . certainly does not pre-exist in the almonds ; it is formed by the action of water upon a peculiar crystallisable substance, called *amygdalin*, aided in a very extraordinary manner by the presence of the pulpy albuminous matter of the seed."
>
> —G. FOWNES, " Elementary Chemistry ", 1850.

Some confusion existed at the time of Scheele as to the identity of acetaldehyde and diethyl ether ; by oxidising alcohol with manganese dioxide and sulphuric acid, Scheele [1] obtained, in 1782, a highly volatile substance which he thought to be ether. It must, however, be remembered that the term ' ether ' had at that time no precise connotation, and was applied indiscriminately to very volatile bodies of pronounced odour ; indeed, Scheele himself shows signs of distinguishing this ' ether ' from the common or ' vitriolated ' ether. Dabit, as long ago as 1800, observed that the ' ether ' prepared in the manner of Scheele from alcohol, manganese dioxide and sulphuric acid, was generated by the removal of part of the hydrogen of the alcohol, and its conversion to water. Fourcroy and Vauquelin,[2] later in the same year, confirmed this view, and clearly distinguished the new volatile principle, from ordinary ether, and from ' nitric ether '. Their remark that " the alcohol does not lose any carbon but only a portion of its hydrogen, which combines with the oxygen of the black oxide of manganese ", is a remarkably accurate expression of the facts. Döbereiner, during 1823–1828, observed that the new ether resinified with alkalies, and that in concentrated form its vapour was suffocating rather than ethereal ; during his researches on platinum-black, he noted that in its presence alcohol and air were capable of giving the new substance. It was during an extension of this work that Liebig [3] observed that two distinct products were formed, a less volatile one which he called acetal, and an extremely volatile and pungent liquid, which he was also able to isolate from the products of oxidation of alcohol with nitric acid. His analyses demonstrated that this new substance contained two atoms of hydrogen less than does the alcohol from which it was produced, thus leading to the name *alcohol-dehydrogenatum*, afterwards abbreviated to *aldehyde*.

The study of the oxidation of methyl alcohol was commenced about the same time as the recognition by Liebig of the nature of aldehyde, but the corresponding oxidation product was not isolated from this source until 1867, when Hofmann [4] prepared it by suspending a red-hot platinum spiral over the surface of methanol ; the combination of the aerial oxygen with the methanol yields sufficient heat to maintain the platinum at a red heat. Formaldehyde had been discovered some years previously by Butlerov [5] in attempts to prepare methylene glycol, $CH_2(OH)_2$ by the hydrolysis of methylene acetate,

$$CH_2(O\,.\,COCH_3)_2.$$

It was, of course, soon realised that the aldehyde from methanol was gaseous at ordinary temperatures, and could be handled conveniently only in solution.

---

[1] Scheele, *Kongl. Vetenskaps Academens Nya Handlingar*, 1782, **3**, 35.

[2] Fourcroy and Vauquelin, *Ann. de Chimie.*, 1800 (1), **34**, 318.

[3] Liebig, *Ann.*, 1835, **14**, 133 ; 1837, **22**, 273.

[4] Hofmann, *Proc. Roy. Soc.*, 1867, **16**, 156.

[5] Butlerov, *Ann.*, 1859, **111**, 242.

Meanwhile, in 1847, Bussy[1] had obtained "œnanthol" (normal heptaldehyde) by the destructive distillation of castor-oil, and benzaldehyde had been known for some considerable time as "oil of bitter almonds". An impetus was given to the study of aldehydes by Wöhler and Liebig's classical memoir, "Investigations on the Radical of Benzoic Acid",[2] from which it was clear that, just as "benzoyl hydride" (or benzaldehyde) is related to benzoic acid, so all acids must have a corresponding aldehyde—or hydride of the radicle.

Acetone, the prototype of ketones, has been known for many centuries. It appears first to have been prepared by the distillation of lead acetate (sugar of lead); Libavius, in 1595,[3] described this mode of preparation, and regarded the product as the "quintessence" of the raw material. Many of the earlier chemists regarded acetone and alcohol as identical, and it remained for the indefatigable Boerhaave, in 1732, to demonstrate the individual nature of acetone. Nearly eighty years elapsed before further work was done on the subject, when the brothers Derosne, and Trommsdorf obtained it by alternative methods. Even when Liebig, in 1832, established its empirical formula, there was still doubt as to its constitution. This appears to have been suggested by Williamson about 1850, and the now accepted view of its structure was confirmed by the synthesis of Freund[4] in 1861; he obtained it by the action of zinc methyl on acetyl chloride.

$$2CH_3 . COCl + Zn(CH_3)_2 \longrightarrow 2CH_3COCH_3 + ZnCl_2.$$

In general, aldehydes and ketones have similar properties, although, as might be expected, the aldehydes are more reactive; it is convenient to regard the aldehydes as a special case of ketone development in that, whereas the ketones arise by development of radicles on both sides of the carbonyl group, with aldehydes this development takes place on one side only.

General Methods of Preparation

As aldehydes may be considered as anhydrides of the extremely unstable 1, 1-glycols:—

$$R . CH(OH)_2 \longrightarrow R . CHO + H_2O$$

methods designed to produce such glycols invariably lead to the formation of aldehydes. Such, for example, is the hydrolysis of dihalides in which two halogen atoms are attached to the same carbon, e.g. by heating ethylidene dibromide with water and a base under pressure, acetaldehyde is obtained:—

$$CH_3 . CHBr_2 + H_2O \longrightarrow CH_3 . CHO + 2HBr$$

or the formation of benzaldehyde when benzal chloride is boiled with milk of lime—a process which serves for its industrial preparation:—

$$C_6H_5 . CHCl_2 + H_2O \longrightarrow C_6H_5 . CHO + 2HCl$$

A variety of methods has been evolved for dehydrogenating primary alcohols to produce the corresponding aldehyde, and this object can be attained either by the use of direct oxidising agents or by catalytic means.

Direct oxidation of the lower primary alcohols can be brought about by manganese dioxide and sulphuric acid, or by chromic acid in the presence of sulphuric acid; for acetaldehyde this mixture is improved[5] by the addition of nitric acid, using a mixture of 10 per cent. sulphuric acid with half its volume of nitric acid (d. 1·42), and one-quarter of its weight of sodium dichromate.

[1] Bussy, *Ann.*, 1847, **60**, 246.

[2] Wöhler and Liebig, *ibid.*, 1832, **3**, 249.

[3] Andreas Libavius, *Alchymia*, 1595.

[4] Freund, *Ann.*, 1861, **67**, 1.

[5] Wertheim, *J.A.C.S.*, 1922, **44**, 2658.

The yield of aldehyde is lowered in cases where the oxidation is carried out in acetic acid by the formation of an acetyl derivative of the enol form of the aldehyde :—

$$R.CH_2.CHO \longrightarrow [R.CH{=}CH.OH] \xrightarrow{AcA} R.CH{=}CH.OAc$$

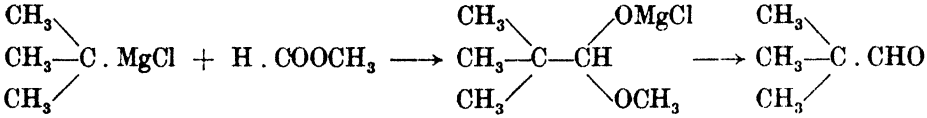
As the carbon chain of the alcohol lengthens, so the amount of aldehyde obtainable by dichromate oxidation alters, increasing up to five carbon atoms and then decreasing as the amount of esters formed increases :—

$$2.R.CH_2OH + O_2 \longrightarrow R.CH_2.O.CO.CH_2R + 2H_2O,$$

and as the volatility of the aldehyde decreases, rendering its escape from the oxidation milieu difficult, and its oxidation to the corresponding acid more certain.

Many higher aldehydes with more than two, and less than ten, carbon atoms may be prepared by the catalytic dehydrogenation of the appropriate primary alcohol. Thus, the best way of obtaining propanal (propionaldehyde) is to pass the vapours of *n*-propyl alcohol through a heated tube packed with brass gauze. The use of so mild a catalyst prevents the reaction from proceeding further.

Various modifications of the Grignard reaction can be adapted to produce aldehydes, particularly those with an α-tertiary carbon atom. Thus, if the Grignard reagent from *ter*-butyl chloride is caused to react at a low temperature

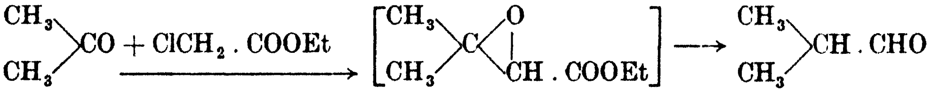


(1)

with an excess of methyl formate, trimethylacetaldehyde is obtained (1). Tschitschibabin [1] used orthoformic ester in a similar manner :—

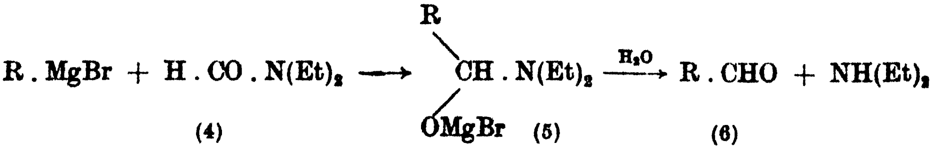
$$(CH_3)_2CHMgI + CH(OC_2H_5)_3 \longrightarrow (CH_3)_2CH.CH(OC_2H_5)_2 \longrightarrow (CH_3)_2CH.CHO$$

and subsequent workers appear to find that the best yields are obtained with ethyl orthoformate.[2] An alternative method of producing an aldehyde of the structure (1) is to allow sodium ethoxide to react with a ketone (acetone, in this case) and ethyl chloroacetate [3] when an unstable ester is obtained (2) which readily splits up into the aldehyde (3) and carbon dioxide :—



(2) (3)

Bouveault [4] has devised a method by which an alkyl bromide, R . Br, may be converted to the aldehyde R . CHO. It is first converted to the Grignard compound, which is allowed to react with a dialkyl substituted formamide, e.g. diethylformamide (4). A compound of the structure (5) is formed, and on boiling with water yields the aldehyde (6).



(4) (5) (6)

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[1] Tschitschibabin, *Ber.*, 1904, **37**, 186.

[2] Smith and Bayliss, *J. Org. Chem.*, 1941, **6**, 437.

[3] Darzens, *C.R.*, 1904, **139**, 1214.

[4] Bouveault, *Bull. Soc. Chem.*, 1904 (iii), **31**, 1183.

Various methods are available for converting acid chlorides to aldehydes. Thus, in 1909, Mauthner[1] observed that an acid chloride could be converted to an acyl cyanide and that the corresponding acid (7) gave the anil of aldehyde (8) on boiling with aniline :—

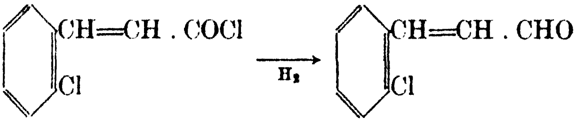
$$\mathrm{R.COCl} \xrightarrow{\mathrm{AgCN}} \mathrm{R.COCN} \longrightarrow \underset{(7)}{\mathrm{R.CO.COOH}}$$

$$\xrightarrow{\mathrm{Ph.NH_2}} \underset{(8)}{\mathrm{R.CH{=}NH.Ph}} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{R.CHO}$$

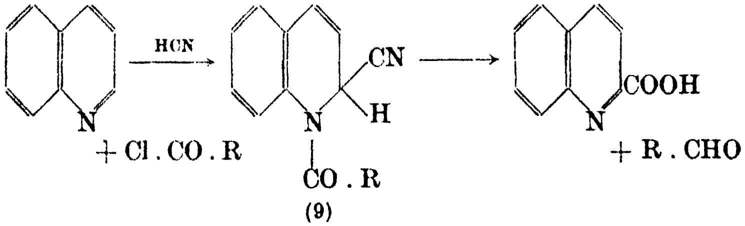
Rosenmund[2] made a marked improvement in this field by demonstrating that acid chlorides in inert solvents can be directly reduced to aldehydes by hydrogen in the presence of catalysts such as palladised barium sulphate, or Raney nickel :—

$$\mathrm{R.COCl} \xrightarrow{\mathrm{H_2}} \mathrm{R.CHO + HCl}$$

In this way benzoyl, butyryl and stearoyl chlorides may readily be converted to the aldehydes ; nuclear chlorine is unaffected, as in the reaction :—



Grosheintz and Fischer[3] discovered that good yields of many aldehydes (including butyryl, n-valeryl, cinnamic and o- and p-methoxy benzaldehydes) can be obtained by allowing the acid chloride to react with quinoline and anhydrous hydrocyanic acid ; a 'cyanhydrin' derivative (9) separates, and is hydrolysed by warming with dilute sulphuric acid, to quinoline carboxylic acid and to aldehyde :—



(9)

The method of Stephen,[4] by which nitriles are reduced by stannous chloride in ether saturated with hydrogen chloride, has proved a valuable addition to the methods available for producing aldehydes.

In essentials, Stephen's method involves the formation and hydrolysis of an imine, although it is probable that it is never isolated except as a stannous chloride complex during the normal course of the reaction :—

$$\mathrm{R.CN} \xrightarrow[\mathrm{ether/HCl}]{\mathrm{SnCl_2\,in}} \mathrm{R.CH{=}NH} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{R.CHO + (NH_4)_2SO_4}$$

In his original memoir Stephen showed the reaction to be generally applicable, obtaining n-octanal, myristaldehyde, palmitaldehyde, stearaldehyde, benzaldehyde, 3, 4, 5-trimethoxybenzaldehyde, and others.

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[1] Mauthner, *Ber.*, 1909, **42**, 188.

[2] Rosenmund *et al.*, *ibid.*, 1918, **51**, 585 ; 594 ; 1923, **56**, 1481.

[3] Grosheintz and Fischer, *J.A.C.S.*, 1941, **63**, 2021.

[4] Stephen, *J.C.S.*, 1925, **127**, 1874.

Mention must also be made of Longman's method [1] for preparing aromatic aldehydes by the action of carbon monoxide on a suspension of anhydrous aluminium chloride in the appropriate aromatic hydrocarbon. This appears to be a variant of the Gattermann reaction (see pp. 215 to 219).

THE SATURATED ALIPHATIC ALDEHYDES

The physical properties of some of the more important members of this series are shown in Table I. Many of them occur naturally in flowers and fruit to the odour of which they contribute considerably. The odour, which is irritant and pungent with formaldehyde and stupefying with acetaldehyde, becomes more agreeable as the molecular weight increases. Nonanal has been isolated from rose, mandarin and lemon oils; decanal from lemon-grass, cassia and iris-root oils, and dodecanal from pine-oil. The synthetically produced 10-, 11- and 12-carbon aldehydes, together with 3-methylnonanal and 3-methyldodecanal are used considerably in perfumery.

TABLE I

SOME SATURATED ALDEHYDES

Systematic name	Formula	M.P.	B.p.	Usual name
Methanal	$H . CHO$	−118°	− 19°	Formaldehyde
Ethanal	$CH_3 . CHO$	−122°	+ 21°	Acetaldehyde
Propanal	$CH_3CH_2 . CHO$	−81°	49°	Propionaldehyde
Butanal	$CH_3(CH_2)_2 . CHO$	—	75°	Butyraldehyde
Pentanal	$CH_3(CH_2)_3 . CHO$	—	103°	*n*-Valeraldehyde
Hexanal	$CH_3(CH_2)_4 . CHO$	—	131°	Capronaldehyde
Heptanal	$CH_3(CH_2)_5 . CHO$	—	153°	Œnanthol
Octanal	$CH_3(CH_2)_6 . CHO$	—	62°/10 mm.	Caprylic aldehyde
Nonanal	$CH_3(CH_2)_7 . CHO$	—	78°/10 mm.	Pelargonaldehyde
Decanal	$CH_3(CH_2)_8 . CHO$	—	92°/10 mm.	Caprinaldehyde *n*-Decylic aldehyde
Undecanal	$CH_3(CH_2)_9 . CHO$	−4°	116°/18 mm.	Undecylaldehyde
Dodecanal	$CH_3(CH_2)_{10} . CHO$	44°	142°/22 mm.	Lauraldehyde
Tetradecanal	$CH_3(CH_2)_{12} . CHO$	23·5°	166°/24 mm.	Myristaldehyde
Hexadecanal	$CH_3(CH_2)_{14} . CHO$	34°	200°/29 mm.	Palmitaldehyde
Octadecanal	$CH_3(CH_2)_{16} . CHO$	63·5°	212°/22 mm.	Stearaldehyde
2-Methylpropanal	$(CH_3)_2CH . CHO$	—	63°	*iso*-Butyraldehyde
2-Methylbutanal	$CH_3 . CH_2CH(CH_3)CHO$	—	92°	Methylethylacetaldehyde
3-Methylbutanal	$(CH_3)_2CH . CH_2 . CHO$	—	92·5°	*iso*-Valeraldehyde
2, 2-Dimethylpropanal	$(CH_3)_3C . CHO$	—	—	Pivalic aldehyde

Formaldehyde (Methanal), H . CHO.—As the initial member of the aldehyde series methanal shows many characteristics which are exceptional when considered in relation to the general behaviour of aldehydes. Its preparation is carried on on a large scale to provide material for the plastics industry (see Appendix II), mainly by the oxidation of methanol, an industry made possible by the cheap and readily available synthetic raw material. The thermodynamic investigation of the reaction

$$CO + H_2 \rightleftharpoons CH_2O$$

by Newton and Dodge [2] show that the reaction is entirely unfavourable to the synthesis of formaldehyde, since even at 300° and 1000 atmospheres the yield of aldehyde would only be 0·8 per cent.

---

[1] Longman, *E.P.*, 1915, 3152.

[2] Newton and Dodge, *J.A.C.S.* 1933, **55**, 4747.

The methanol oxidation process is carried out on a very large scale, about 700,000,000 lb. being produced annually. The reaction has been most carefully studied and interested readers are referred to a summary by Homer ;[1] careful control of catalyst, temperature and pressure of reaction are necessary to ensure optimum yields, largely by preventing the further decomposition of the product to carbon monoxide and hydrogen.

An alternative process for formaldehyde production is the controlled oxidation of the simple paraffin hydrocarbons. Thus, methane is readily oxidised in this way

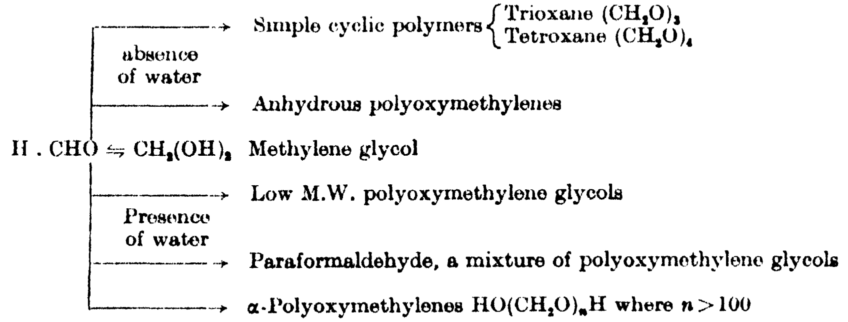
$$CH_4 + O_2 \longrightarrow CH_2O + H_2O$$

The process has been claimed by Russian investigators[2] to yield 70 per cent. of the aldehyde. Under suitably controlled oxidation conditions ethane, propane and butane also yield substantial amounts of formaldehyde, so that natural gas offers an alternative source of this product. The process has been used industrially in U.S.A.[3] The biological formation of formaldehyde, as an intermediate in the phytochemical synthesis of carbohydrates, is discussed in Appendix II to this chapter. Industrial formaldehyde solutions (' Formalin ') contain about 37 per cent. w/w. of the aldehyde calculated as CH_2O, and 10 per cent. of methanol, which stabilises the aldehyde.

Formaldehyde is intensely reactive, and is seldom encountered in its monomeric form ; it readily transposes into a variety of polymers, and even in aqueous solution is instantaneously hydrated to methylene glycol. These changes are summarised in Table II.

TABLE II

POLYMERIC FORMS OF FORMALDEHYDE


Simple cyclic polymers
Trioxane (CH₂O)₃
Tetroxane (CH₂O)₄
absence of water
Anhydrous polyoxymethylenes
H . CHO ⇋ CH₂(OH)₂ Methylene glycol
Low M.W. polyoxymethylene glycols
Presence of water
Paraformaldehyde, a mixture of polyoxymethylene glycols
α-Polyoxymethylenes HO(CH₂O)ₙH where n > 100

That formaldehyde in solution is first converted to methylene glycol was shown by Staudinger,[4] who isolated the glycol as a thick syrup by extracting formalin solutions with ether at low temperatures, and by various observers of the physical properties of the so-called formaldehyde solutions, who pointed out[5] that in the U.V. absorption and Raman spectra, the characteristic lines of the carbonyl group were absent.

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[1] Homer, *J. Soc. Chem. Ind.*, 1941, **60**, 213T.

[2] Mayor, *l'Ind. Chim.*, 1939, **26**, 291.

[3] Walker, U.S.P. (1935), 2,007, 115 and 2,007, 116 ; (1936), 2,042, 134 ; (1939), 2,153,526 ; (1940), 2,186,688.

[4] Staudinger, " Die Hochmolecularen Organischen Verbindungen " (J. Springer), Berlin, 1932.

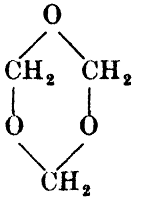
[5] Schou, *J. Chem. Phys.*, 1929, **26**, 72.

Three types of formaldehyde polymerisation * are recognised, two linear and one cyclic. Thus, the two linear forms may be represented as

$$\ldots CH_2{-}O{-}CH_2{-}O{-}CH_2{-}O{-}CH_2{-}O{-}CH_2 \ldots$$

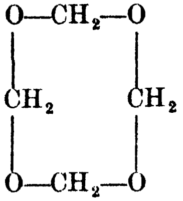
and $\ldots CH(OH) . CH(OH) . CH(OH) . CH(OH) \ldots$

whilst the cyclic forms are almost invariably



Trioxane

or



Tetroxane

The second linear form is associated with carbohydrate structure, and is, therefore, considered separately (see Chap. VIII). In the case of the polyoxymethylene glycols, the end-groups of the chain are hydroxyls, and the structures involved are shown below :—

Dioxymethylene glycol	$HO . CH_2 . O . CH_2 . OH$
Trioxymethylene glycol	$HO . CH_2 . O . CH_2 . O . CH_2 . OH$
Tetraoxymethylene glycol	$HO . CH_2 . O . CH_2 . O . CH_2 . O . CH_2 . OH$
Higher polyoxymethylene glycols	$HO . (CH_2O)_n . H$

Some of the smaller ($n = 2$–12) polyoxymethylene glycols have been isolated and examined ; [1] the acetone solubility of these glycols decreases as n increases, the dodecaoxymethylene glycol being only slightly soluble in the boiling solvent. It will have been observed by the reader that the generic formula $HO(CH_2O)_nH$ implies that these glycols are constituted as n molecular proportions of formaldehyde with one of water ; the percentage of " formaldehyde " (calculated as CH_2O) in each will vary from 77 per cent. in the case of the dioxy-compound through 93 per cent. in the case of the octo-oxy-compound, to figures approximating to 100 per cent. when n is very large. Industrial ' paraformaldehyde ' is a mixture of polyoxymethylene glycols with an average percentage of CH_2O of 95–96 ; in such a mixture it is probable that n varies from 8 to 100.

Butlerov, the discoverer of formaldehyde, also first prepared paraformaldehyde ; he considered it, on account of its apparent vapour density, to be dioxymethylene $(CH_2O)_2$; Hofmann, however, recognised that the vapour produced was that of monomeric formaldehyde, and based his conclusions that the new substance was ' trioxymethylene ' $(CH_2O)_3$, on an ambiguous analogy with the thio-derivative. The name " trioxymethylene ", although erroneous, has been consistently used for paraformaldehyde ; its use should be abandoned as likely to cause confusion with the true trioxymethylene or trioxan (see p. 350). Paraformaldehyde is usually prepared by vacuum distillation of the aqueous formaldehyde solutions, when water with a little methanol passes over and solid paraformaldehyde remains in the still. Paraform is a convenient source of monomeric formaldehyde in the laboratory, being readily decomposed to the monomer on heating.

The polyoxymethylenes are classified by the Greek letters, in the absence of any other simple distinguishing mark. They are :—

α-Polyoxymethylene.—A high polymer containing almost 100 per cent. of

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* The term " polymer " should, strictly, represent only those compounds the empirical formulæ of which are exact multiples of that of the monomer. By common consent it has here been extended to cover structures including a small proportion of combined water.

[1] Staudinger, *loc. cit.*

CH_2O. It is prepared by the action of acids or alkalies on aqueous formaldehyde solutions, and is characterised by being almost insoluble in water; prolonged treatment with water causes depolymerisation and solution.

β-Polyoxymethylene.—Is obtained in minute, short, thick hexagonal prisms by mixing five volumes of industrial formalin with two of concentrated sulphuric acid and allowing the mixture to cool. The crystals retain a little acid, but it is doubtful whether this is other than mechanically entrapped. The β-form is characterised by the ease with which it gives a crystalline sublimate. It is readily soluble in sodium sulphite solution.

γ-Polyoxymethylene.—If in the preparation of the β-form, the addition of acid is so regulated and combined with external cooling that the temperature does not rise above 20°, a mixture of the β- and γ-forms separates. They are separated by dissolving out the β-form in a solution of sodium sulphite. The γ-form is a colourless crystalline product unaffected by sulphite solutions. It is not a true polyoxymethylene, but arises from the etherification of the terminal hydroxyl groups of polyoxymethylene glycols of high molecular weight by the methanol present in industrial formalin. Its structure may, therefore, be represented as :—

$$CH_3O\,.\,(CH_2O)_n\,.\,CH_3 \text{ where } n \text{ is } 300\text{–}500$$

δ-Polyoxymethylene.—When the γ-form is boiled for some time in water, the terminal groups undergo a rearrangement which results in the structure

$$CH_3O\,.\,CH_2O\,.\,CH_2O\,\ldots\,CH_2O\,.\,CH_2CH(OH)\,.\,OCH_3$$

The product forms a white micro-crystalline powder.

ε-Polyxymethylene.—When trioxan is repeatedly subjected to sublimation from the same container, an insoluble residue accumulates, a white silky, amorphous substance melting with decomposition at 195–200°. The structure of this substance is unknown.

eu-Polyoxymethylene.—This substance is formed when pure, anhydrous, monomeric formaldehyde is allowed to polymerise. Its formula is $(CH_2O)_n$, where n is of the order of 5000. It is quite different in its physical properties from all other polymeric forms of formaldehyde, being elastic and capable of film and fibre formation. On warming, eu-polyoxymethylene shows plasticity, but it gives an X-ray pattern indicating a crystalline internal arrangement.

Trioxan has already been discussed as a cyclic ether (p. 350); tetroxan, or tetraoxymethylene, was prepared by Staudinger[1] by heating a high M.W. polyoxymethylene diacetate. It is a crystalline compound, m. 112°, and shows a stability similar to that of trioxan.

THE REACTIONS OF FORMALDEHYDE

Butlerov, in his original investigations on formaldehyde, observed its almost quantitative reaction with ammonia to form the crystalline hexamethylenetetramine (Hexamine) $(CH_2)_6N_4$. Industrially, hexamine is prepared by saturating formalin with gaseous ammonia and vacuum-evaporating the solution to the point of crystallisation; the centrifuged and washed crystals are the industrial grade of hexamine, containing about 0·3 per cent. of water and a little mineral ash (usually less than 0·2 per cent.). Recrystallisation from water containing a little ammonia gives a product which, for all practical purposes, may be considered pure.

The formation of hexamine from formaldehyde and ammonia must, of course, take place by a series of reactions, the course of which has given rise to much speculation. The initial formation of methylene imine (10) appears in almost all suggested courses of reaction, but whether this substance immediately polymerises to trimethylenetriamine (11) or reacts with a further quantity of formaldehyde, as methylene glycol, giving the hydroxy-imine (12) is not clear.

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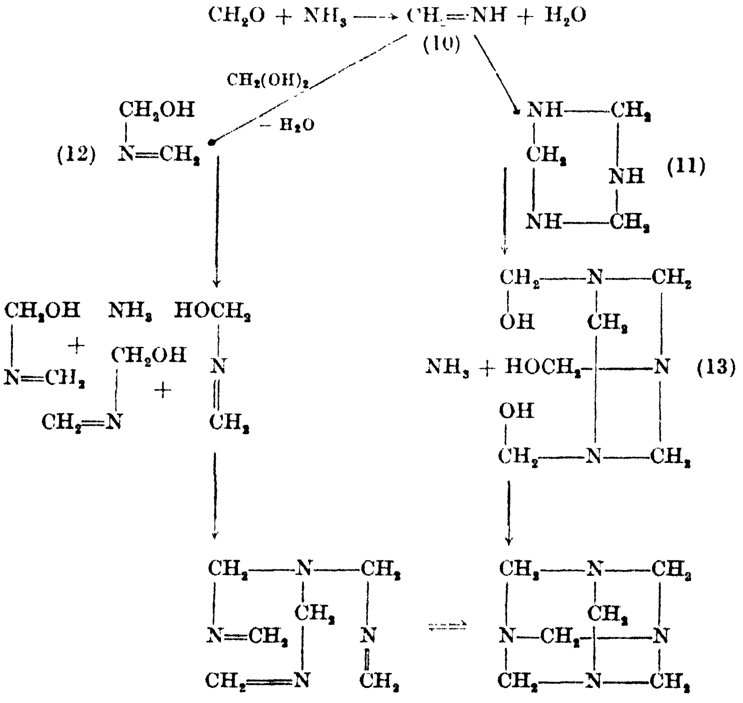
[1] Staudinger, *H. Chim. Acta.*, 1925, **8**, 65.

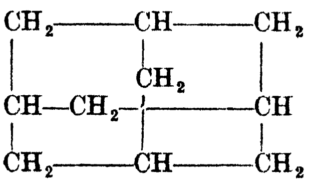
TABLE III

Formation of Hexamine



Lösekann's structure.[1] Duden and Scharff's structure.[2]

If the former be true then subsequent reaction with formaldehyde would, according to Baur and Ruetschi,[3] give trimethylol trimethylene triamine (13) and this by further reaction with ammonia, hexamine itself. If, however, the secondary product is the hydroxy-imine, three molecules of this could react with ammonia to give hexamine (as in Lösekann's formulation). The symmetrical



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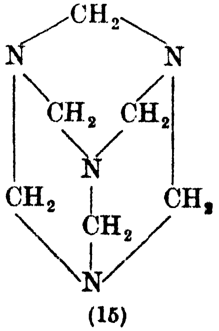

(15)

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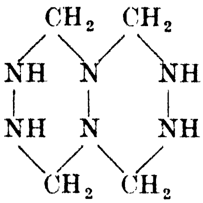
[1] Lösekann, *Chem. Ztg.*, 1890, **14**, 1409.

[2] Duden and Scharff, *Ann.*, 1895, **288**, 218.

[3] Baur and Ruetschi, *H. Chim. Acta.*, 1941, **24**, 754.

formula proposed about fifty years ago by Duden and Scharff, is commonly accepted, and is supported by X-ray examination. It makes hexamine a derivative (by nitrogen substitution) of the hydrocarbon adamantane (*q.v.*) (14). It is clear, however, that the Lösekann structure is closely related to this form, and could readily pass into it. Hexamine is frequently written as in (15), but X-ray data show that the structure is probably analogous to that shown in Fig. 96, p. 130. The chemical properties of hexamine are further discussed in Vol. II.

When formaldehyde reacts with hydrazine an insoluble compound is formed which is reported to have the structure (16), although no formal proof of this has been forthcoming.



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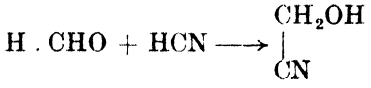
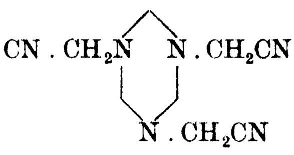


$$H.CHO + HCN \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CN \end{array}$$

(17)



(18)

Formaldehyde reacts easily with hydrogen cyanide,[1] to form the nitrile of glycollic acid (17), but if the acid is replaced by sodium cyanide and ammonium chloride, the substance methylene aminoacetonitrile is formed, probably as the trimer (18).

Formaldehyde reacts with almost all common inorganic reagents such as halogens, halides, acids, hydrogen peroxide, hydrogen sulphide, sulphur dioxide, etc. The more important of these reactions are described below.

A most unusual type of reaction takes place with alkaline hydrogen peroxide, in which hydrogen and an alkali formate are obtained :—

$$2CH_2O + H_2O_2 + 2NaOH \longrightarrow 2H.COONa + 2H_2O + H_2$$

This liberation of hydrogen was made the basis of a method for the estimation of formaldehyde by Blank and Finkenbeiner.[2] Under neutral conditions the methylolperoxides are formed :—

Monomethylol peroxide, $HOCH_2OOH$.—An oil, $[n_D]_{16^\circ}$ 1·4205, exploding violently on heating.

Dimethylol peroxide, $HOCH_2.OO.CH_2OH$.—A crystalline product, m. 62–65°, obtained originally by Fenton[3] by evaporating solutions of formaldehyde and hydrogen peroxide. It ignites in contact with iron, copper oxide, or platinum black.

bis-(*Dimethylol*) *peroxide*, $HOCH_2OCH_2.O.O.CH_2OCH_2OH$.—An oil.

The reaction of hydrogen sulphide on formaldehyde depends on the acidity of the solution ; in acid solutions a crystalline product,[4] m. 97–103°, is obtained ; in neutral solutions, oily substances of the series $HOCH_2SH$, $HSCH_2.O.CH_2SH$, $HSCH_2SCH_2.O.CH_2SH$ are formed.

On the other hand, in strongly acid solutions, the so-called trithian, or trithioformaldehyde is obtained, an odourless crystalline compound (from benzene), m. 218°. Its great stability and normal vapour density lend support to its formulation as the trimeric cyclic structure (18a) analogous to trioxan.

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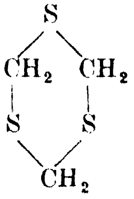
[1] Henry, *C.R.*, 1890, **110**, 759.

[2] Blank and Finkenbeiner, *Ber.*, 1898, **31**, 2979.

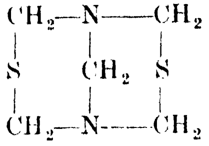
[3] Fenton, *Proc. Roy. Soc.* (A), 1914, **90**, 492.

[4] Baumann, *Ber.*, 1890, **23**, 60.

LeFèvre[1] showed that when formaldehyde and ammonium sulphide interact, a substance having the structure (19) is obtained.



(18a)



(19)

Sodium bisulphite and formaldehyde unite to give a crystalline product which has been used industrially for a variety of purposes, under the name 'sodium formaldehyde bisulphite'. The work of Raschig and Prahl,[2] and of Lauer and Langkammerer[3] has shown this substance to be the methylol sulphonic acid salt, $HOCH_2 . SO_3Na$. It is readily reduced to the corresponding "sulphoxylate", $HO . CH_2 . SO_2Na$, which is itself a powerful reducing agent, and is used as a bleaching and stripping agent in textile dyeing, and as a reducing agent in the preparation of dye-vats.

The characteristic and irritating smell of formaldehyde can be detected at concentrations as low as ten parts per million. Formaldehyde is a valuable germicide and antiseptic, and is used as such in considerable quantities; several of the polymers are equally effective, due to their slow reversion to the monomer in aqueous suspensions.

Reactions of Formaldehyde with Hydroxylic Compounds.—When formaldehyde solutions are mixed with methanol, or the gaseous monomer is passed into methanol, a strongly exothermic reaction takes place with the formation of a hemiacetal :—

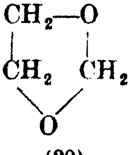
$$CH_2O + CH_3OH \rightleftharpoons CH_3O . CH_2OH$$

Such hemiacetals are unstable, and tend to revert, on heating, into the component molecules; on the other hand, the presence of a trace of mineral acid, or of ferric or zinc chlorides, the reaction proceeds further with the formation of the formaldehyde acetals (called 'formals') :—

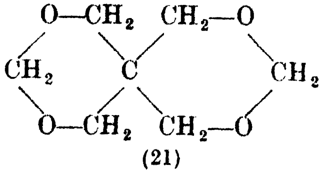
$$CH_2O + 2CH_3OH \longrightarrow CH_3O . CH_2 . OCH_3 + H_2O$$

The formals are typical ethers in that they preserve a high chemical stability, although they are more readily hydrolysed in acid solutions than are the simple ethers. The simplest formal, methylal, $CH_2(OCH_3)_2$, is available in industrial quantities being obtained by the controlled oxidation of methanol at low temperatures, and in the presence of acid catalysts. It is clear that the mechanism of its formation under these conditions is the oxidation of a moiety of the methanol to formaldehyde which reacts with the excess of methanol. The commoner formals are listed in Table IV.

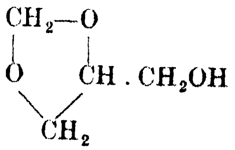
Stable cyclic formals are obtained when formaldehyde reacts with glycols and other polyhydroxy compounds. Typical examples are dioxolan (20), the



(20)



(21)



(22)

compound from ethylene glycol, a stable liquid, b. 76°, an excellent solvent,

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[1] LeFèvre and LeFèvre, *J.C.S.*, 1932, 1142.

[2] Raschig and Prahl, *Ann.*, 1926, **448**, 265.

[3] Lauer and Langkammerer, *J.A.C.S.*, 1935, **57**, 2360.

TABLE IV

SOME FORMALS

Formal	Formula	B.P.
Dimethyl	$CH_2(OCH_3)_2$	42°
Methylethyl	$CH_3O . CH_2 . OC_2H_5$	67°
Diethyl	$CH_2(OC_2H_5)_2$	89°
Dipropyl	$CH_2(OC_3H_7)_2$	141°
Di*iso*propyl	$CH_2(OCH(CH_3)_2)_2$	119°
Di*iso*butyl	$CH_2(OC_4H_9)_2$	164°
Di*ter*butyl	$CH_2(OC(CH_3)_3)_2$	184°
Di*iso*amyl	$CH_2(OC_5H_{11})_2$	207°
Diallyl	$CH_2(OCH_2CH{=}CH_2)_2$	138°
Dibenzyl	$CH_2(OCH_2C_6H_5)_2$	280°

miscible with water in all proportions. With pentaerythritol an extremely stable *spiro*- compound (21) is formed, m. 50°, b. 280°, the systematic name for which is " 2, 4, 8, 10 tetroxaspiro [5.5] hendecane ". The action of formaldehyde on glycerol yields several products, of which the most abundant is the formal (22).

Carbohydrates readily give formals when treated with formaldehyde ; in the case of simple monoses and their corresponding alcohols, such as mannitol and sorbitol, the products are cyclic ; with bioses such as sucrose, maltose and lactose it is probable that steric factors induce the formation of hemiacetals.[1]

Formaldehyde, in the presence of concentrated halogen acids, is capable of a combined halogenating and alkylating action,[2] as in :—

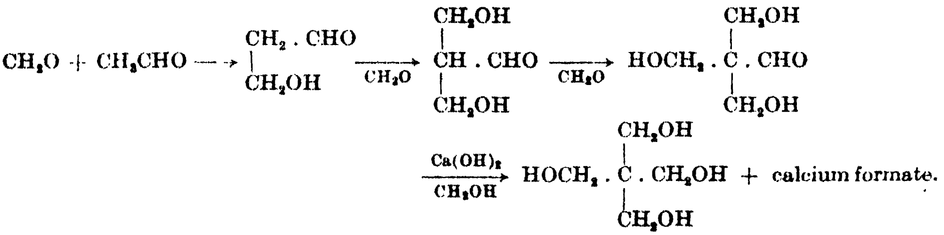
$$R . OH + CH_2O + HCl \longrightarrow R . O . CH_2Cl + H_2O$$

With methanol the compound obtained is chloromethyl methyl ether, $CH_3O . CH_2Cl$ (b. 59·7°) ; Hill and Keach [3] have extended the reaction to a series of compounds. It may be added that the reaction persists even with long-chain alcohols, e.g. cetyl alcohol, which gives cetyloxymethyl bromide

$$C_{16}H_{33}OH + CH_2O + HBr \longrightarrow C_{16}H_{33}OCH_2Br$$
$$C_{16}H_{33}OCH_2Br + N(CH_3)_3 \longrightarrow [C_{16}H_{33}OCH_2N(CH_3)_3]Br \ (23)$$

(= cetyl bromomethyl ether). This on treatment with tertiary bases, such as trimethylamine, gives long-chain quaternary compounds, e.g. cetyloxymethyltrimethylammonium bromide (23). Such compounds have specialised detergent and antiseptic properties.

One of the most important reactions of formaldehyde is that with acetaldehyde, in the presence of calcium hydroxide when pentaerythritol is formed. This reaction, discovered in 1891 by Tollens and Wiegand,[4] is the basis of the large scale manufacture of pentaerythritol, now widely used for explosive (tetranitrate), alkyd resin and drying oil manufacture. The reaction appears to follow the course :—



$$CH_2O + CH_3CHO \longrightarrow \begin{matrix}CH_2 . CHO\\ |\\ CH_2OH\end{matrix} \xrightarrow[CH_2O]{} \begin{matrix}CH_2OH\\ |\\ CH . CHO\\ |\\ CH_2OH\end{matrix} \xrightarrow[CH_2O]{} HOCH_2 . \begin{matrix}CH_2OH\\ |\\ C . CHO\\ |\\ CH_2OH\end{matrix}$$

$$\xrightarrow[CH_2OH]{Ca(OH)_2} HOCH_2 . \begin{matrix}CH_2OH\\ |\\ C . CH_2OH\\ |\\ CH_2OH\end{matrix} + \text{calcium formate.}$$

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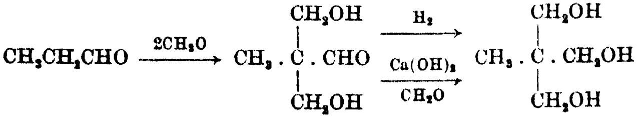
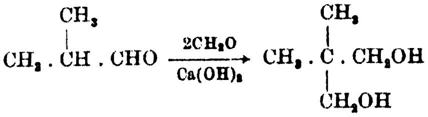
[1] Contardi and Ciocca, *Rend. inst. lombardo. sci.*, 1936, **69**, 1057 (*C. Abs.*, 1939, **33**, 4583).
[2] Henry, *Bull. classe. sci. Acad. roy. Belg.*, 1893 (3), **25**, 439.
[3] Hill and Keach, *J.A.C.S.*, 1926, **48**, 259.
[4] Tollens and Wiegand, *Ann.*, 1891, **265**, 316.

Higher aldehydes also give polyhydroxy compounds ; thus, propionaldehyde gives both pentaglycerose (24) and pentaglycerol (25), whilst *iso*-butyraldehyde yields pentaglycol (26).



$$CH_3CH_2CHO \xrightarrow{2CH_2O} CH_3.C(CH_2OH)_2.CHO \; (24) \xrightarrow[Ca(OH)_2]{H_2} \xrightarrow{CH_2O} CH_3.C(CH_2OH)_3 \; (25)$$

(24) (25)



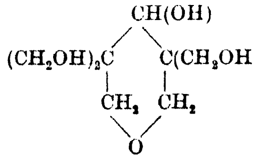
$$CH_3.CH(CH_3).CHO \xrightarrow[Ca(OH)_2]{2CH_2O} CH_3.C(CH_3)(CH_2OH)_2$$

(26)

Ketones, both open-chain and cyclic, react similarly with formaldehyde, giving compounds which are analogous to pentaerythritol. Thus, acetone, which might be expected to give the enneaheptitol (27), does in actual fact give the anhydro form (28), which is closely related to the γ-pyrones, and, in particular, to the γ-pyrone (29) isolated during the same reaction.

$(CH_2OH)_3C.CH(OH).C(CH_2OH)_3$

(27)



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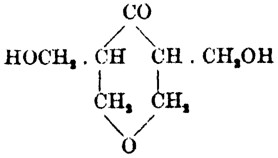


(29)

The reaction of formaldehyde with phenols, ureas and amines is discussed in Appendix II to this chapter.

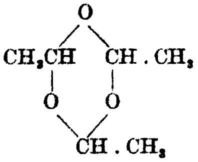
Acetaldehyde, CH_3CHO.—Acetaldehyde is produced in small quantities in most fermentations, in the conduct of which it plays an important part ; nearly all such processes give a fore-run during the subsequent distillation which is rich in acetaldehyde and acetal. The bulk of acetaldehyde used industrially is obtained from acetylene, by catalytic hydration in the presence of a mercury salt :—

$$HC{\equiv}CH + H_2O \xrightarrow[H_2SO_4]{HgO} CH_2{=}CHOH \longrightarrow CH_3.CHO$$

This process is more fully discussed on page 111.

Acetaldehyde has a penetrating and overpowering smell, said to resemble that of apples. It is miscible with water in all proportions, and like formaldehyde polymerises easily, although the polymers formed from it are simpler in structure than the polyoxymethylenes.

If a trace of sulphuric acid is added to acetaldehyde, it rapidly changes exothermically to paraldehyde (30) or trimethyltrioxymethylene, a clear liquid, m. 10·5°, b. 124°. The compound was first obtained by Fehling in 1838,[1] and has been used as a soporific for many years. When heated with a little sulphuric acid acetaldehyde is regenerated ; this is probably the most convenient way of obtaining supplies of acetaldehyde in the laboratory for synthetic work.



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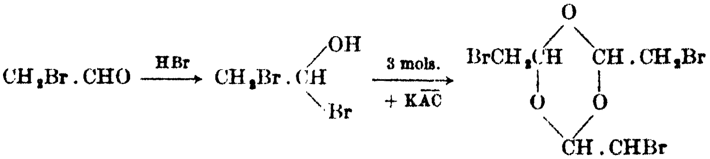

(31) (32) (33)

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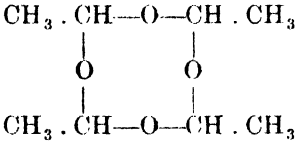
[1] Fehling, *Ann.*, 1838, **27**, 319.

The formation of cyclic trimers from aldehydes is a general reaction, and probably takes place by the catalyst forming an addition compound at the carbonyl group, followed by a trimolecular or sequential elimination. The formation of such a compound[1] has been demonstrated with bromo-acetaldehyde (31), which yields a stable HBr-addition compound (32), and this in turn, when treated with potassium acetate, gives tribromoparaldehyde (33).

If acetaldehyde be treated with a trace of sulphur dioxide or mineral acid, without the temperature being allowed to rise above 0°, a tetramer is formed, and the whole solidifies to a crystalline mass of metaldehyde. This substance



(34)

forms long, shining prisms which sublime at 115°, and are during the process partially reconverted to acetaldehyde. Pauling and Carpenter[2] have made a study of the X-ray spectrum of metaldehyde which fully upholds the cyclic structure (34). Metaldehyde has been used as a convenient smokeless, solid fuel, and as a slug-killer.

The tendency which acetaldehyde shares with other simple aldehydes of undergoing a species of dimerisation, gives rise to the 'aldol' condensation, one of the more important reactions of synthetic organic chemistry. In the simplest instance

$$CH_3.CHO + CH_3.CHO \xrightarrow[NaOH]{dil.} CH_3.CH(OH).CH_2CHO$$

(35)

aldol (35) is obtained, usually in mildly alkaline solutions. Only by careful control of conditions, and adjustment of alkalinity can the aldol condensation be made to stop at the formation of the true aldol; dehydration readily takes place, in the case of aldol itself to crotonaldehyde (36).

$$\left|\begin{array}{l} CH_3.CH(OH).CH_2.CHO \\ CH_3.CH{=}CH.CHO(36) + CH_3.CHO \\ CH_3.CH{=}CH.CH(OH).CH_2.CHO \\ CH_3.CH{=}CH.CH{=}CH.CHO + CH_3CHO \\ CH_3.CH{=}CH.CH{=}CH.CH(OH).CH_2.CHO \\ \text{etc., etc.} \end{array}\right.\downarrow$$

This new aldehyde very readily enters into a further aldol condensation with acetaldehyde and, as shown above, the sequence of dehydration and aldolisation being repeated, until finally an aldehyde-resin is obtained.

The generic principle involved in an aldol condensation is based on the reactivity of the hydrogen atoms attached to carbon, which is itself adjacent to a carbonyl group. One or all of such "α-hydrogens" can react in this way, and they need not, necessarily, be furnished by a second molecule of the same aldehyde; the α-hydrogen may be that of another aldehyde, a ketone, a ketonic ester, a nitrile, or a nitroparaffin, etc.; indeed, the formation of pentaerythritol referred to (p. 389) under "formaldehyde" is an excellent example of heterogeneous aldol formation, followed by reduction of the aldehyde group when no further α-hydrogen atoms remain. It will be realised, therefore, that the permutations of the aldol condensation are almost innumerable, and cover a wide variety of organic types.

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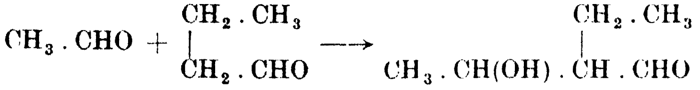
[1] **Stepanov, Preobraschenski and Schtschukina, *Ber.*, 1926, 59, 2533.**

[2] **Pauling and Carpenter, *J.A.C.S.*, 1936, 58, 1274.**

If two different aldehydes, 'a' and 'b', are used, four possible aldols can be obtained—'aa', 'ab', 'ba', and 'bb'. As a general rule[1] only one compound is to be found in substantial yield, namely, that in which the larger molecule furnishes the α-hydrogen for aldol condensation with the smaller, thus :—

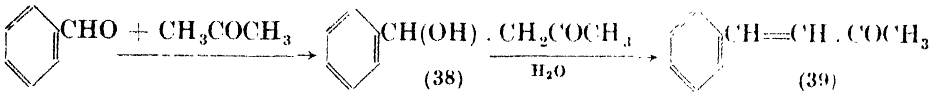


$$CH_3 . CHO + \begin{array}{l} CH_2 . CH_3 \\ | \\ CH_2 . CHO \end{array} \longrightarrow \begin{array}{r} CH_2 . CH_3 \\ | \quad\quad\; \\ CH_3 . CH(OH) . CH . CHO \end{array}$$

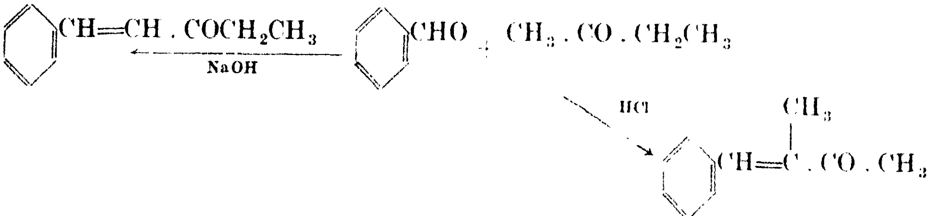
(37)

When acetaldehyde and *n*-butyraldehyde are the two aldehydes in question, the product is substantially 2-ethyl-3-hydroxybutanal (37).

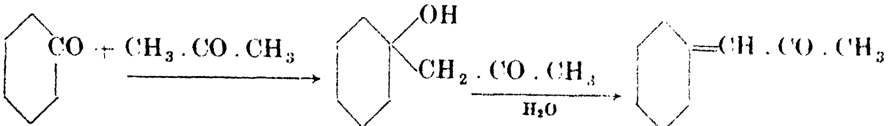
Where one of the pair, in an aldol condensation, is a ketone, two important generalisations emerge; that the ketone almost invariably furnishes the α-hydrogens, and that dehydration of the aldol is almost certain to take place before the aldol itself can be isolated. Thus, when benzaldehyde reacts with acetone, the aldol (38) almost immediately dehydrates to give the unsaturated ketone (39). If the acetone in the last reaction be replaced by an unsymmetrical ketone such as methylethyl ketone, the two possible unsaturated ketones which can be formed, assuming that the ketone will provide the α-hydrogens, are each present in the final product; but the proportions of either can be made very large, according to the catalyst used :—



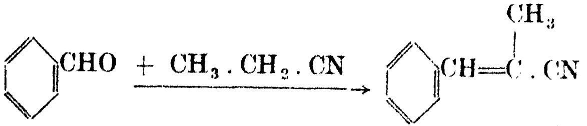
(38) (39)

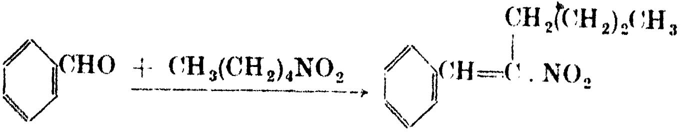


Two ketones can seldom be induced to yield an 'aldol'; but acetone and cyclohexanone react thus :—



When the activating group is —CN or —NO_2, there is no ambiguity as to the course of the reaction, although in many cases the isolation of the intermediate hydroxyl compound presents difficulties, owing to the marked tendency towards dehydration. Two typical examples, of considerable potential synthetic value, are given below :—





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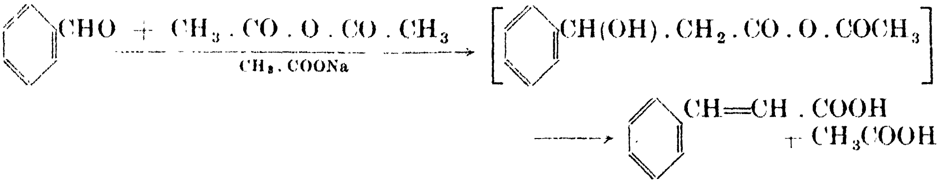
[1] Harries and Muller, *Ber.*, 1902, **35**, 966.

If the α-hydrogen for this type of condensation be provided by an acid anhydride, the reaction follows the course set out below, and constitutes the well-known Perkin reaction, discovered by W. H. Perkin (Senr.) in 1877[1] :—



Perkin himself held that it was the anhydride which reacted; Fittig[2] contested that it was the sodium acetate, and this view was held for a long time. The full story of the principles underlying the Perkin reaction is discussed in Vol. III: it is sufficient here to refer the reader to the excellent summary given by Breslon and Hauser[3] as a prelude to their own experiments in this field.

Both oxidation and reduction of acetaldehyde are easily brought about catalytically. Air and acetaldehyde vapour are converted almost quantitatively to acetic acid when passed over a manganous oxide catalyst. If a solution of acetaldehyde in air-free water is treated with finely divided palladium, oxidation to acetic acid takes place, the palladium acting as a receptor for the hydrogen, until saturated, when the reaction stops. If air be now bubbled through the solution the palladium-hydrogen complex is restored to palladium and the reaction can proceed.

Riley, Morley and Friend[4] showed that the reaction

$$CH_3.CHO + SeO_2 \longrightarrow (CHO)_2 + Se + H_2O$$

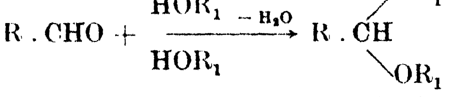
proceeds almost quantitatively at 60–80°, and that this unusual oxidation provides an excellent method for preparing considerable quantities of glyoxal. The reaction is general and affects only the α-hydrogens relative to the existing —CHO group.

Acetaldehyde is one of the few aldehydes which, on account of the activity of the α-hydrogens, is unable to give the Cannizzaro reaction in its original form. The action, however, of aluminium ethoxide in catalytic quantities leads to the formation of ethyl acetate in good yield, presumably by the reactions

$$2CH_3CHO \xrightarrow[Al(OEt)_3]{H_2O} CH_3CH_2OH + CH_3COOH \xrightarrow[-H_2O]{} CH_3CH_2.OCOCH_3.$$

This reaction is used industrially for the direct production of ethyl acetate from the readily accessible acetaldehyde obtained by the hydration of acetylene.

The effect of stoichiometric quantities of aluminium ethoxide is to reduce the aldehydes to alcohols.[5] The formation of acetals from acetaldehyde and alcohols proceeds normally according to the course :—



$$R.CHO + \begin{matrix} HOR_1 \\ HOR_1 \end{matrix} \xrightarrow{-H_2O} R.CH\begin{matrix} OR_1 \\ OR_1 \end{matrix}$$

and the formation of such compounds has been made the subject of extensive studies by Adkins.[6] Acetaldehyde behaves normally in this respect, and with ethanol forms what is commonly called 'acetal', $CH_3CH(OEt)_2$ a valuable starting material for synthesis.

---

[1] Perkin, *J.C.S.*, 1877, **31**, 389.

[2] Fittig, *Ber.*, 1881, **14**, 1824; Fittig, *Ann.*, 1885, **227**, 48; Fittig and Slocum, *ibid.*, 53.

[3] Breslon and Hauser, *J.A.C.S.*, 1939, **61**, 786 and 793.

[4] Riley, Morley and Friend, *J.C.S.*, 1932, 1875.

[5] Meerwein and Schmidt, *Ann.*, 1925, **444**, 221.

[6] For a bibliography, see *J.A.C.S.*, 1934, **56**, 442.

One of the more important groups of reactions associated with aldehydes, and well illustrated by the behaviour of acetaldehyde, are those concerned with the formation of nitriles. When acetaldehyde is converted to its bisulphite compound and the latter allowed to react with sodium cyanide, lactonitrile (40) is obtained ;

$$CH_3\,.\,CHO + NaHSO_3 \longrightarrow CH_3CH(OH)SO_3Na \xrightarrow[NaCN]{} \underset{(40)}{CH_3CH(OH)CN}$$

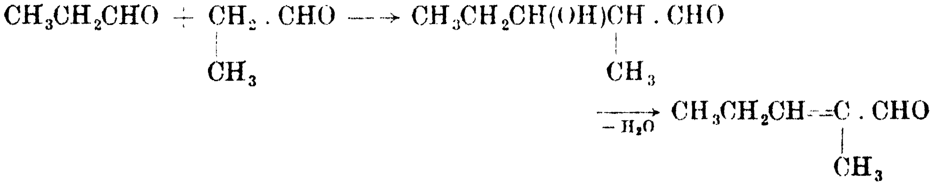
$$\xrightarrow[C_2H_5OH]{H_2SO_4} CH_3CH(OH)COOEt$$

this, treated with ethanol and sulphuric acid is directly converted to ethyl lactate, a valuable lacquer solvent. If the reaction with cyanide is allowed to take place in the presence of ammonium chloride, an amino-nitrile is obtained, which yields alanine when hydrolysed :—

$$CH_3CHO + NaCN + NH_4Cl \longrightarrow CH_3\,.\,CH(NH_2)CN \longrightarrow CH_3\,.\,CH(NH_2)COOH.$$

Higher Aldehydes.—In general, higher aldehydes with a straight chain exhibit properties similar to those of acetaldehyde, their reactivity becoming more sluggish as the molecular weight increases. The presence of a branched chain leads to differences in reactivity consequent on the presence of an additionally active hydrogen atom.

Propanal (Propionaldehyde), CH_3CH_2CHO, is fairly readily obtained by the chromic oxidation of *n*-propyl alcohol, but if required in considerable quantity is best obtained by Bouveault's method, the direct vapour-phase dehydrogenation of the alcohol with copper oxide. In many of the general reactions of aldehydes, propanal reacts through the α-carbon atom, but the aldol condensation is readily followed by dehydration :—



$$CH_3CH_2CHO + \underset{\displaystyle CH_3}{\underset{|}{CH_2}}\,.\,CHO \longrightarrow CH_3CH_2CH(OH)\underset{\displaystyle CH_3}{\underset{|}{CH}}\,.\,CHO \xrightarrow[-H_2O]{} CH_3CH_2CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\,.\,CHO$$

Butanal (butyraldehyde), $CH_3CH_2CH_2CHO$, is obtained in considerable quantities industrially, by the differential catalytic reduction of crotonaldehyde. Its synthesis from acetaldehyde, therefore, follows the course :—

$$CH_3CHO + CH_3CHO \longrightarrow CH_3CH(OH)CH_2CHO \longrightarrow CH_3CH{=}CH\,.\,CHO \longrightarrow CH_3CH_2CH_2CHO.$$

Pentanal, (n-valeraldehyde), $CH_3(CH_2)_3CHO$, can be obtained by the oxidation of *n*-amyl alcohol, now available industrially, but much amyl-*n*-valerate is formed at the same time. Bouveault's method is preferable as a means of dehydrogenating *n*-amyl alcohol, but is only successful with this and higher aldehydes when carried out under reduced pressure. An excellent account of the application of the method to the preparation of *n*-nonanal is given by Lewinsohn.[1]

Reference has already been made to the preparation of heptanal (œnanthol) by the dry distillation of castor oil under reduced pressure,[2] when it is obtained together with undecylenic acid. It is a liquid of pungent odour, and is a valuable starting point in organic synthesis.

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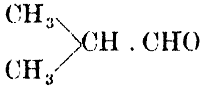
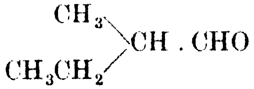
[1] Lewinsohn, *Perf. Ess. Oil Record*, 1924, **15**, 13.

[2] Bussy, *Ann.*, 1846, **40**, 246.

Branched chain aldehydes, of which *iso*-butyraldehyde (41) is the prototype, are made from the corresponding alcohols, either by chromic oxidation or by catalytic dehydrogenation. The yields are lower than with normal aldehydes, due to the presence of an additional group on the α-carbon atom, which enhances the reactivity of the α-hydrogen atom, leading to some dehydration.

The arborescent aliphatic aldehydes most commonly encountered are *iso*-butyraldehyde, 2-methyl butanal (42) and 2, 2-dimethylpropanal (pivalic aldehyde or trimethylacetaldehyde) (43). The latter is obtained in excellent yield by dehydrogenating *neo*-pentyl alcohol.


(41)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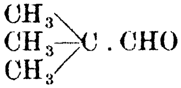

(43)

Unsaturated Aldehydes

In Table V some of the more commonly encountered unsaturated aldehydes are listed. Of these, acrolein and crotonaldehyde are industrially available, although the former, on account of its instability, is usually used *in situ*.

TABLE V

Some Unsaturated Aldehydes

Systematic name	Structure	B.P.	Usual name
2-Propenal	$CH_2{=}CH . CHO$	52°	Acrolein (m. p. – 87°)
2-Butenal	$CH_3CH{=}CH . CHO$	104°	Crotonaldehyde
2-Hexenal	$CH_3CH_2CH_2CH{=}CH . CHO$	47°/17 mm.	—
2-Propyl-2-propenal	$CH_2{=}CH(C_3H_7)CHO$	117°	α-Propylacrolein
2-*iso*-Butyl-2-propenal	$CH_2{=}CH(C_4H_9)CHO$	133°	α-*iso*-Butylacrolein
2-Amyl-2-propenal	$CH_2{=}CH(C_5H_{11})CHO$	59°/13 mm.	α-Amylacrolein
2-Methyl-2-butenal	$CH_3 . CH{=}C(CH_3)CHO$	116°	Tiglic aldehyde. Guaiol.
2-Methyl-2-pentenal	$CH_3CH_2CH{=}C(CH_3)CHO$	137°	Methyl ethylacrolein
2, 6-Nonadien-1-al	$CH_3(CH_2)_2CH{=}CH(CH_2)_2CH{=}CH . CHO$	94°/2 mm.	—
2-Propynal	$CH{\equiv}C . CHO$	59°	Propargylaldehyde
2-Butynal	$CH_3 . C{\equiv}C . CHO$	107°	Tetrolaldehyde
2-Octynal	$CH_3(CH_2)_4C{\equiv}C . CHO$	89°/26 mm.	Amylpropiolaldehyde
2-Nonynal	$CH_3(CH_2)_5C{\equiv}C . CHO$	91°/13 mm.	Hexylpropiolaldehyde

Acrolein (*2-Propenal*), $CH_3{=}CH . CHO$ was obtained by several early investigators during the destructive distillation of fats, albeit in an impure form. Brandes, about 1820, gave a sample of the crude material obtained from the destructive distillation of coconut oil to Berzelius who, in spite of its impure condition, recognised it as an aldehyde and named it "acrolein". Redtenbacher[1] showed that acrolein was not produced when fatty acids alone were distilled, and concluded that the aldehyde arose from glycerol, a hypothesis which he proceeded to put to the test by heating glycerol with dehydrating agents, thus disclosing a method of preparing acrolein which after the lapse of over a century is still in use.

Glycerol is usually dehydrated with potassium hydrogen sulphate :—

$$CH_2OH . CHOH . CH_2OH \xrightarrow{-2H_2O} CH_2{=}CH . CHO,$$

---

[1] Redtenbacher, *Ann.*, 1843, **47**, 113.

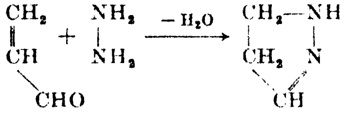
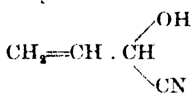
but Bergh[1] showed that a more satisfactory method was to heat glycerol with sodium chloride and orthophosphoric acid.

Acrolein is a limpid liquid of a most powerful odour and lachrymatory character ; it is readily soluble in water and is characterised by an extreme tendency to polymerisation, a substance, disacryl, being produced by this operation. The rate of polymerisation can be slowed by the addition of small quantities of polyhydric phenols—hydroquinone is usually chosen. The polymerisation is accelerated by light.

Acrolein also forms a trimer, ' metacrolein ' which appears to be analogous in structure to trioxymethylene, and paraldehyde. It is a crystalline solid, m. 45°, and is obtained by warming 3-chloropropanal with alkali (38). Some of the reactions of acrolein are listed in Table VI.

TABLE VI

SOME REACTIONS OF ACROLEIN

Reagent	Product
Air	Autoxidation to acrylic acid $CH_2{=}CH\,.\,COOH$
Hydrogen	Catalytic reduction with $Ni + H_2$ yields propanal and propanol-1 successfully
Alcohol	Adds to the double bond as well as forming the acetal, giving : $C_2H_5O\,.\,CH_2CH_2CH(OC_2H_5)_2$
Halogen acids	Add in opposition to the so-called Rule of Markownikov, giving β-halopropionic acids
Bromine	Gives the αβ-dibromo derivative (2, 3-dibromopropanal) ; but in the presence of water bromine gives glyceric aldehyde
Phosphorus pentachloride	Gives $CH_2{=}CH\,.\,CHCl_2$
Ammonia	Readily absorbed by acrolein to give ' acrolein-ammonia ' $[C_3H_4O]_2NH_3$ which is of doubtful structure, but on heating yields β-picoline
Hydrazine	Condenses readily to pyrazoline 
Baryta-water	Yields α-acrose (a mixture of *d*- and *l*-fructose)
Hydrogen cyanide	Gives the normal cyanhydrin :— 

Crotonaldehyde.—When Lieben[2] heated acetaldehyde in salt solution he obtained a new compound to which he gave the rather uninspired name of ' aldehyde-ether ' ; Bauer[3] obtained a similar product from the action of zinc, chloride on aldehyde, but it remained for Kekulé[4] in 1872 to demonstrate the identity of the products of the two previous investigators and to determine the structure of the product as crotonaldehyde. Since that time crotonaldehyde,

---

[1] Bergh, *J. Pr. Chem.*, 1909, **79**, 351.

[2] Lieben, *Ann.* (Suppl.), 1861, **1**, 117.

[3] Bauer, *Ann.*, 1861, **117**, 142.

[4] Kekulé, *ibid.*, 1872, **162**, 92 ; 309

$CH_3CH{=}CH\,.\,CHO$ has been obtained by a variety of methods; by the action of heat on aldol in the presence of a trace of iodine,[1] when an 80 per cent. conversion is attained. Industrially, crotonaldehyde is obtained by the absorption of acetylene in sulphuric acid of a controlled strength followed by dilution of the solution with water; curiously enough, this method was discovered in 1877 [2] but has only come into prominence recently.

Crotonaldehyde has an irritating odour, less powerful than that of acrolein, and with a fruity note. Its reactions also resemble those of acrolein, but the presence of the conjugated system permits the hydrogen of the methyl group to take part in aldol condensations. Thus, with acetaldehyde it yields 2, 4-hexadien-al (44) and 2, 4, 6-octatrien-al (45) by the reactions set out below. The hexadienal is more usually known as sorbic aldehyde.[3]

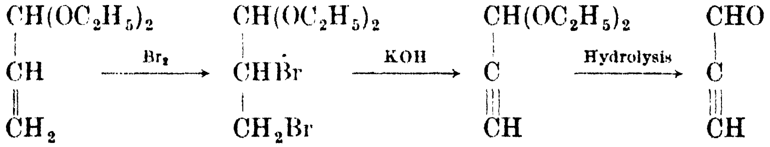
$$\begin{array}{lll} (a) & CH_3CH{=}CH\,.\,CHO + CH_3\,.\,CHO & \Big\downarrow\ H_2O \\ & CH_3CH{=}CH\,.\,CH{=}CH\,.\,CHO & \end{array}$$

(44)

$$\begin{array}{lll} (b) & CH_3CH{=}CH\,.\,CHO + CH_3CH{=}CH\,.\,CHO & \Big\downarrow\ H_2O \\ & CH_3CH{=}CH\,.\,CH{=}CH\,.\,CH{=}CH\,.\,CHO & \end{array}$$

(45)

Of the higher unsaturated aldehydes, several occur naturally, thus 2-hexenal is found in most green leaves, and gives to them their characteristic odour; Koolhaas [4] found 2-dodecenal, $CH_3(CH_2)_8CH{=}CH\,.\,CHO$ in the leaves of a species of sea-holly (*Eryngium fœtidum*), and Späth and Kesztler [5] showed that the characteristic odour of violet leaves was, in part, due to 2, 6-nonadienal, $CH_3CH_2CH{=}CH(CH_2)_2CH{=}CH\,.\,CHO$. The arborescent aldehydes of the citral group are to be discussed later in the section entitled 'olefinic terpenes'. Several of the aldehydes of the acetylene series are quite well known; the initial member of the series, propynal, $CH{\equiv}C\,.\,CHO$, is obtained by the addition of bromine to acrolein acetal, giving 2, 3-dibromo acrolein acetal (46); solid potash converts this to the acetal of propynal (47), and the aldehyde itself (48) is obtained by hydrolysis of the acetal with saturated tartaric acid solution :—



(46) (47) (48)

$$\begin{array}{c} CH(OC_2H_5)_2 \\ | \\ CH \\ \| \\ CH_2 \end{array} \xrightarrow{Br_2} \begin{array}{c} CH(OC_2H_5)_2 \\ | \\ CHBr \\ | \\ CH_2Br \end{array} \xrightarrow{KOH} \begin{array}{c} CH(OC_2H_5)_2 \\ | \\ C \\ ||| \\ CH \end{array} \xrightarrow{Hydrolysis} \begin{array}{c} CHO \\ | \\ C \\ ||| \\ CH \end{array}$$

The higher members of the acetylenic aldehyde series may be obtained either by Moureu's method, in which the sodium derivative of an acetylene is allowed to react with ethyl formate :—

$$CH_3(CH_2)_4C{\equiv}C\,.\,Na + H\,.\,COOC_2H_5 \longrightarrow CH_3(CH_2)_4C{\equiv}C\,.\,CHO + NaOC_2H_5$$

or by an analogous process using a Grignard reagent and orthoformic ester, thus :—

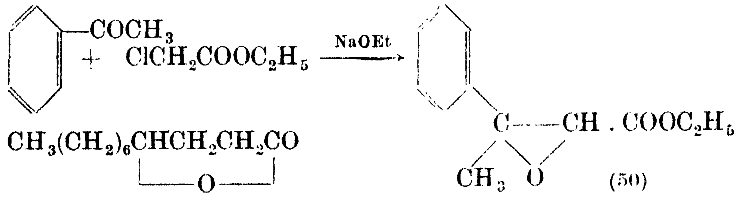
$$CH_3CH_2C{\equiv}CH + CH_3MgI \longrightarrow CH_3CH_2C{\equiv}C\,.\,MgI \xrightarrow{CH(OC_2H_5)_3}$$

$$\longrightarrow CH_3CH_2C{\equiv}C\,.\,CH(OC_2H_5)_3 \xrightarrow{H^\bullet} CH_3CH_2C{\equiv}C\,.\,CHO.$$

---

[1] Hibbert, *J.A.C.S.*, 1915, **37**, 1748.
[2] Lagermark and Eltekov, *Ber.*, 1877, **10**, 637.
[3] Kuhn and Hoffer, *ibid.*, 1930, **63**, 2164.
[4] Koolhaas, *Rec. Trav. Chim.*, 1932, **51**, 460.
[5] Späth and Kesztler, *Ber.*, 1934, **67**, 1496.

Some mention should be made of the so-called 'Aldehyde C14' and 'Aldehyde C16', which under the names 'peach' and 'strawberry' aldehydes are used in flavouring. They are not aldehydes; the 'C14' is γ-undecalactone (49) and the 'C16' is methyl phenylglycidic ethyl ester (50); the latter compound is obtained by condensing acetophenone with chloroacetic ester in the presence of sodium ethylate:—

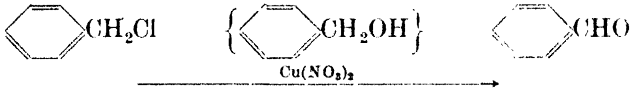


(49)

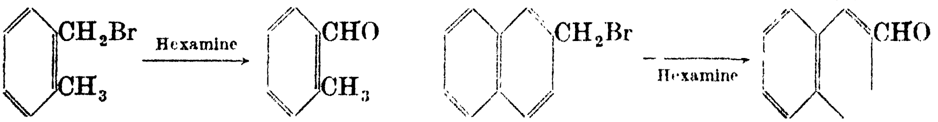
(50)

Cyclic and Aromatic Aldehydes

Reference was made, in the introduction to this chapter, to the early history of benzaldehyde; this type of aldehyde may be obtained by the action of oxidising agents on aryl compounds with a chloromethyl or bromomethyl side-chain. The simplest instance is that of benzyl chloride, which when boiled with a solution of copper nitrate, is both hydrolysed and oxidised, giving benzaldehyde—presumably through the intermediate formation of benzyl alcohol:—



Recent work shows that this reaction is a general one, and may be more expeditiously and economically performed by heating the bromomethyl compound with hexamine. Thus, ω-bromo-*o*-xylene (51) gives a good yield of *o*-tolylaldehyde (52), whilst Hewitt[1] used this method to obtain the otherwise inaccessible 1-bromo-2-naphthaldehyde (54) from 1-bromo-2-bromomethyl naphthalene (53):—



(51) (52) (53) (54)

The direct hydrolysis of benzal chloride with milk of lime is readily able to give benzaldehyde, but the difficulty of obtaining pure benzal chloride leads to a benzaldehyde of indifferent purity.

One of the best ways of obtaining benzaldehyde in a pure state is to pass a stream of air through boiling dibenzyl when oxidation takes place:—

$$C_6H_5 . CH_2CH_2 . C_6H_5 \longrightarrow 2C_6H_5 . CHO.$$

The yield is good, and the benzaldehyde is pure after a single rectification to remove some benzoic acid which is always formed at the same time.

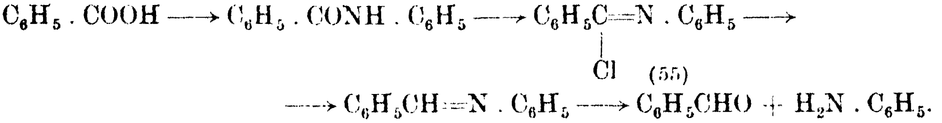
The direct conversion of toluene to benzaldehyde was first carried out by Etard[2] in 1877, using chromyl chloride in an indifferent solvent such as chloroform or carbon disulphide. An intermediate is formed which is highly explosive, but which, on decomposition with water yields the aldehyde in excellent yield. A more convenient method of direct oxidation is to suspend the toluene an an excess of 98 per cent. sulphuric acid and carry out the oxidation with cerium dioxide. Industrially toluene is often oxidised to benzaldehyde with sulphuric acid and manganese mud (largely MnO_2) in the presence of catalytic quantities of copper sulphate.

---

[1] Hewitt, *J.C.S.*, 1940, 297.

[2] Etard, *C.R.*, 1877, **84**, 127.

Reduction of the carboxyl group of benzoic acid to an aldehyde group is not so easy, but can be accomplished by converting the acid through its anilide to the iminochloride (55) with phosphorus pentachloride, and allowing this to react with Stephen's reagent (stannous chloride in ether saturated with hydrogen chloride); the sequence of reactions is represented thus :—



$$C_6H_5 . COOH \longrightarrow C_6H_5 . CONH . C_6H_5 \longrightarrow C_6H_5\underset{\displaystyle Cl}{\underset{|}{C}}{=}N . C_6H_5 \longrightarrow$$

(55)

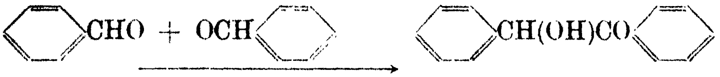
$$\longrightarrow C_6H_5CH{=}N . C_6H_5 \longrightarrow C_6H_5CHO + H_2N . C_6H_5.$$

Benzaldehyde is a colourless oil, with a characteristic odour of bitter almonds. Pure benzaldehyde is not easily oxidised by atmospheric oxygen at ordinary temperatures, but in the presence of traces of heavy metals, or of water or acids it readily absorbs oxygen being converted to benzoic acid.

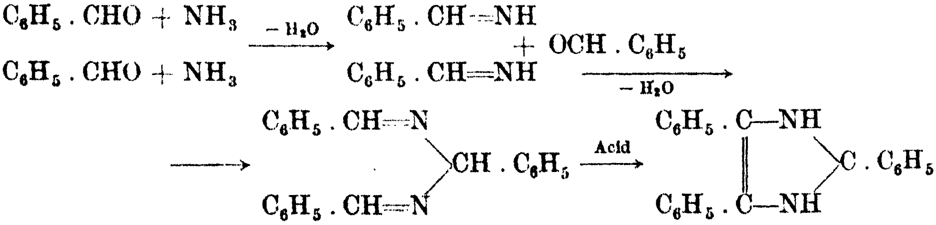
Like aliphatic aldehydes benzaldehyde readily gives the Cannizzaro reaction,[1] and it was the 'disproportionation' of this aldehyde

$$2C_6H_5 . CHO \xrightarrow[KOH]{H_2O} C_6H_5 . CH_2OH + C_6H_5 . COOK,$$

that led this investigator to study the reaction, which is general and is given by most alkyl, nitro- and halogen substituted derivatives of benzaldehyde. It is worthy of note that the method by which this reaction is now carried out in the laboratory, namely, by emulsifying the aldehyde with very concentrated aqueous alkali is due to Meyer[2]; Cannizzaro used alcoholic alkali which resinified both the benzyl alcohol and part of the benzaldehyde. One reaction which characterises aromatic aldehydes is the benzoin condensation, by which two molecular proportions of, say, benzaldehyde condense to give an α-hydroxy ketone, such as benzoin :—



This, again, is a general reaction, and both it and the Cannizzaro reaction have given rise to much speculation as to their precise mechanism (see Vol. II). With ammonia, benzaldehyde reacts in a manner which does not resemble the formation of aliphatic aldehyde-ammonia complexes, a substance 'hydrobenzamide'—for want of a more accurate name—being formed :—



(56) (57)

Hydrobenzamide (56) is readily converted by heating in acid solution to the bitter triphenyldihydroglyoxaline, amarin (57).

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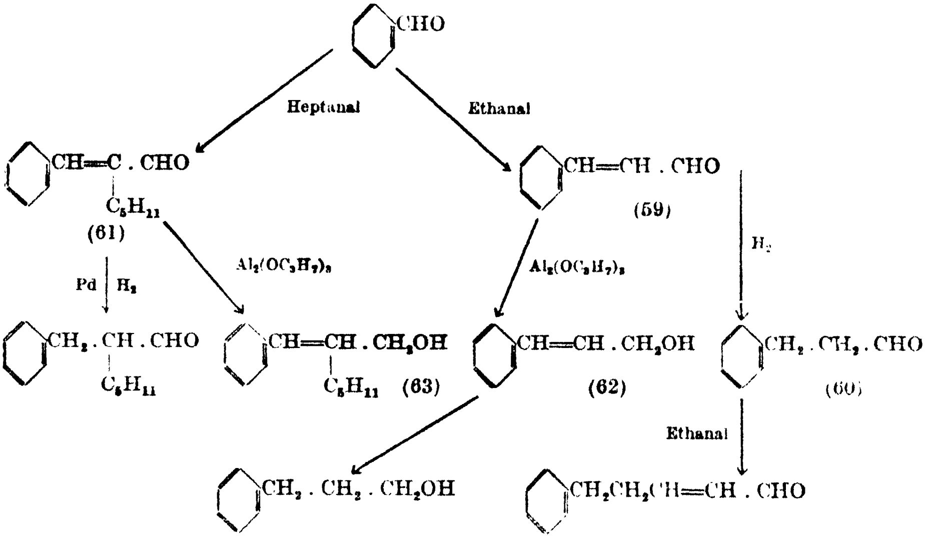
[1] Cannizzaro, *Ann.*, 1853, **88**, 129.

[2] Meyer, *Ber.*, 1886, **19**, 2394.

Benzaldehyde can take part in the majority of aldol type condensations, and gives rise to products which are of great value in perfumery. Thus, with acetaldehyde, cinnamaldehyde (59) is formed, and may easily be reduced to the rose-perfumed phenylpropionaldehyde (60). Higher aliphatic aldehydes condense through their α-carbon atom, thus heptanal gives amylcinnaminic aldehyde (61). Whilst normal reducing agents saturate the double-bond of these aldehydes, aluminium alkoxides reduce the aldehyde group to the alcohol group, leaving the double bond untouched. Thus, aluminium *iso*propoxide reduces cinnamic aldehyde to cinnamic alcohol (62) and amylcinnamic aldehyde to amylcinnamic alcohol (63). The esters of many of these alcohols are valuable perfumery chemicals. Some of these transformations are outlined in Table VII.

TABLE VII



For preparing the homologues of benzaldehyde various modifications of the Friedel-Crafts and Gattermann-Koch reactions are available, many of which are detailed in the Appendix to Chapter III. Some of the homologous aldehydes are listed in Table VIII.

TABLE VIII

SOME AROMATIC ALDEHYDES

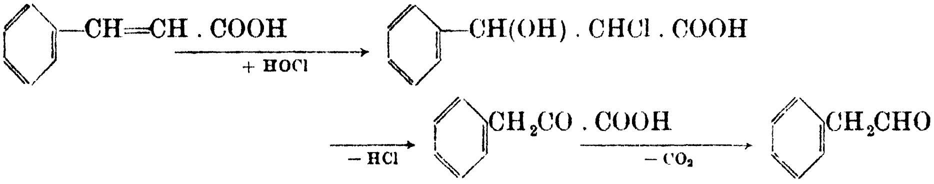
Name	Formula	B.P.
o-Toluic aldehyde	$CH_3C_6H_4 . CHO$ (1, 2)	200°
m-Toluic aldehyde	$CH_3 . C_6H_4 . CHO$ (1, 3)	199°
p-Toluic aldehyde	$CH_3 . C_6H_4 . CHO$ (1, 4)	204°
2, 4-Dimethylbenzaldehyde	$(CH_3)_2C_6H_3 . CHO$ (1, 2, 4)	215° (m. — 9°)
2, 5-Dimethylbenzaldehyde	$(CH_3)_2C_6H_3 . CHO$ (1, 2, 5)	220°
3, 4-Dimethylbenzaldehyde	$(CH_3)_2C_6H_3 . CHO$ (1, 3, 4)	226°
3, 5-Dimethylbenzaldehyde	$(CH_3)_2C_6H_3 . CHO$ (1, 3, 5)	221°
2, 4, 5-Trimethylbenzaldehyde	$(CH_3)_3C_6H_2 . CHO$ (1, 2, 4, 5)	121°/10 mm. (m. 43·5°)
2, 4, 6-Trimethylbenzaldehyde	$(CH_3)_3C_6H_2 . CHO$ (1, 2, 4, 6)	237°
3, 4, 5-Trimethylbenzaldehyde	$(CH_3)_3C_6H_2 . CHO$ (1, 3, 4, 6)	— (m. 52°)
α-Naphthaldehyde	$C_{10}H_7 . CHO$	292°
β-Naphthaldehyde	$C_{10}H_7 . CHO$	— (m. 61°)
2-Phenanthraldehyde	$C_{14}H_9 . CHO$	— (m. 59°)
3-Phenanthraldehyde	$C_{14}H_9 . CHO$	— (m. 80°)
9-Phenanthraldehyde	$C_{14}H_9 . CHO$	— (m. 101°)

The aldehydes of naphthalene, phenanthrene and complex ring systems are almost invariably prepared from the nitrile by the method of Stephen, or by the Rosenmund reduction of the acid chlorides. The early preparation of naphthaldehydes was carried out by the distillation of intimate mixtures of the calcium salts of formic and naphthoic acids :—

$$C_{10}H_7 . COOca + H . COOca \longrightarrow C_{10}H_7CHO + CaCO_3.$$

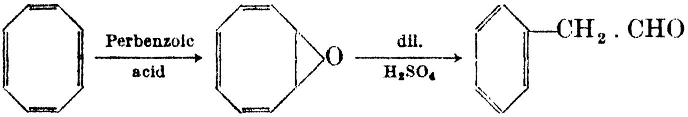
The development of chloromethyl derivatives of the higher hydrocarbons, tends to make the corresponding aldehyde more readily accessible, by using the hexamine reaction. Thus, from 2-chloromethyl naphthalene, 2-naphthaldehyde is readily obtained by heating with hexamine and acetic acid for about 30 seconds ; slight dilution with hot water gives a solution from which naphthaldehyde separates on cooling.

Mixed aralkyl aldehydes in which the aldehyde group is situated in the side-chain are known in considerable number. Of the saturated aldehydes of this class, phenyl acetaldehyde (64) is important as a perfumery substance of pronounced hyacinth odour. It has been made from cinnamic acid, by the action of hypochlorous acid followed by rearrangement and decarboxylation :—



(64)

but can now be made by converting the readily available *cyclo*-octatetrene (65) to its oxide (66) with perbenzoic acid ; the oxide is converted quantitatively to phenyl acetaldehyde on treatment with a few drops of dilute sulphuric acid.

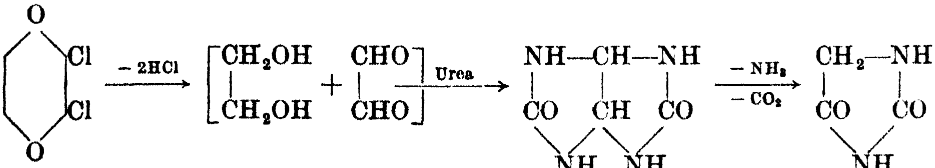


(65) (66)

Di- and Tri-Aldehydes

Glyoxal, CHO . CHO, is the initial member of the series of aliphatic dialdehydes and appears to have been first described by Debus in a series of papers[1] on the oxidation of alcohol, aldehyde and similar substances. Lübavin[2] described a simple method of obtaining glyoxal by the oxidation of alcohol with nitric acid, but the yield is small ; recently it has been shown that by heating ethanol or acetaldehyde with selenium dioxide, a good yield of glyoxal is obtained. This process has made the material available industrially.

Butler and Cretcher[3] showed that the dichloro-dioxan shown in (67) is a



(67) (68) (69)

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[1] Debus, *Ann.*, 1856, **100**, 5 ; 1857, **102**, 20 ; 1858, **107**, 199 ; 1859, **110**, 199 ; 1861, **118**, 253.

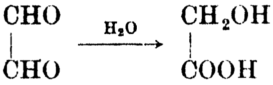
[2] Lübavin, *Ber.*, 1875, **8**, 768 ; 1877, **10**, 1366.

[3] Butler and Cretcher, *J.A.C.S.*, 1932, **54**, 2987.

potential source of glyoxal. Thus, when heated with an aqueous solution of urea it gives a good yield of glycoluril (68), and this on hydrolysis is converted into hydantoin (69).

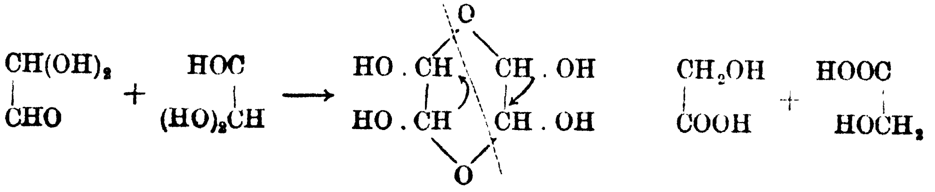
When prepared by any of the methods set out above glyoxal is obtained in a white, crystalline, polymeric form. The monomer can be obtained by distilling the polymer with a little phosphorus pentoxide, when it is obtained as a pungent green vapour condensing to yellow crystals, m. 15°; b. 50°. It soon polymerises to a colourless form.

In its reactions glyoxal resembles the ordinary aldehydes except that it has no α-hydrogen atom capable of entering into condensation reactions. One of the most interesting properties of glyoxal is its ability to undergo an internal Cannizzaro reaction when stirred with aqueous alkali, glycollic acid being obtained :—



$$\begin{array}{c}CHO\\|\\CHO\end{array}\xrightarrow{H_2O}\begin{array}{c}CH_2OH\\|\\COOH\end{array}$$

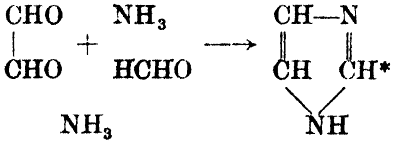
The mechanism of this reaction has been much studied, as it may throw light on the progress of the Cannizzaro reaction with ordinary aldehydes. It appears that most aldehydes and all di-aldehydes are capable of existing in the hydrated or α, α-diol form, and the suggestion has been made that the internal Cannizzaro reaction of glyoxal takes place through the partial diol which forms a semi-acetal, thus :—



(70)

This theory involves the assumption that tetrahydroxy dioxane (70) will break down quantitatively to glycollic acid, and will be discussed in detail in Vol. III.

Debus [1] showed that if glyoxal is warmed to 70° with aqueous ammonia glyoxaline (imidazole) (71) is formed. In this reaction the source of the single carbon marked * is a matter for speculation. The yield is increased if formaldehyde is added to the mixture :—



(71)

Attempts to prepare *malonic aldehyde*, $CH_2(CHO)_2$ have been mainly unsuccessful, the instability of the compound being such that it can only be obtained in aqueous solution, and then probably as the enol form,

$$HO.CH{=}CH.CHO,$$

since the solution is acid in reaction. The starting point for preparing malonic aldehyde is acrolein, which gives rise to the following sequence of reactions :—

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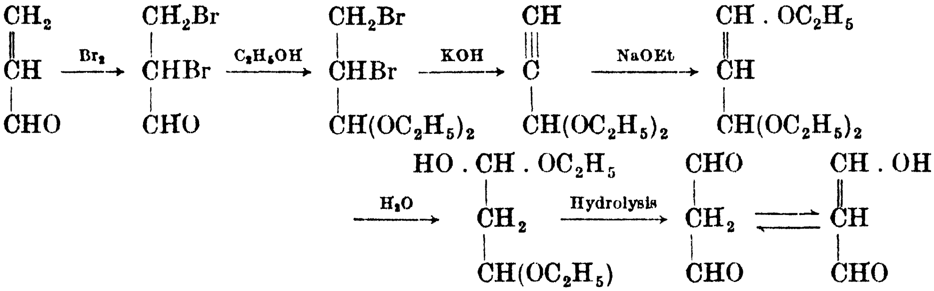
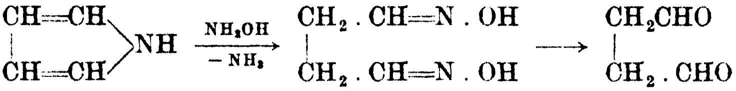
[1] Debus, *loc. cit.*



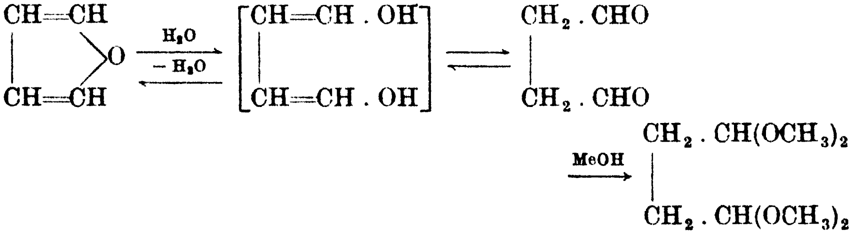
Succindialdehyde, butane-1, 4 dial, OCH . CH_2CH_2 . CHO, one of the most interesting and valuable of the aliphatic dialdehydes, is one of the most difficult to prepare. The accepted method for its preparation is the reaction of alcoholic hydroxylamine with pyrrole, when the dioxime (72) is obtained ; a yield of 40–50 per cent. is practicable.



(72) (73)

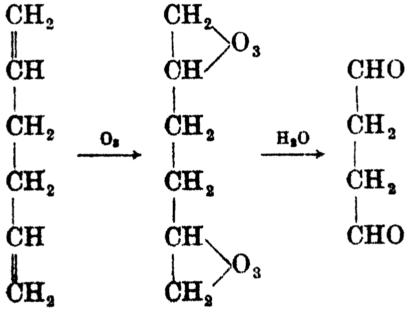
The conversion of the dioxime to the dialdehyde (73) is a difficult task. Mannich and Budde [1] recommend the decomposition of a dioxane suspension of the dioxime with ethyl nitrite, by which about 60 per cent. of the monomeric aldehyde can be obtained as a liquid b. 67°/13 mm. It polymerises on standing to a glass-like form. Other methods for obtaining succindialdehyde are based

(*a*) on the alcoholysis of furan by hydrogen chloride in methanol, whereby the tetra-acetal of succindialdehyde is obtained :—



This inter-relation of succindialdehyde and furan is reversible, and was used by Harries [2] to establish the structure of furan.

(*b*) The hydrolysis of the diozonide of diallyl has been shown to yield succindialdehyde, but the reaction does not appear to have more than an academic interest :—



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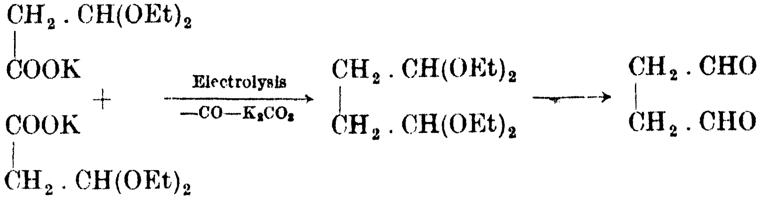
[1] Mannich and Budde, *Arch. Pharm.*, 1932, **270**, 283

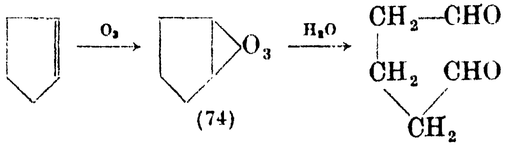
[2] Harries, *Ber.*, 1901, **34**, 1496.

(*c*) Wohl and Schweitzer[1] obtained the tetraethylacetal of succindialdehyde by the electrolysis of the potassium salt of ββ-diethoxypropionic acid :—



$$\begin{array}{l} CH_2\,.\,CH(OEt)_2 \\ | \\ COOK \\ \qquad + \\ COOK \\ | \\ CH_2\,.\,CH(OEt)_2 \end{array} \xrightarrow[-CO-K_2CO_3]{\text{Electrolysis}} \begin{array}{l} CH_2\,.\,CH(OEt)_2 \\ | \\ CH_2\,.\,CH(OEt)_2 \end{array} \longrightarrow \begin{array}{l} CH_2\,.\,CHO \\ | \\ CH_2\,.\,CHO \end{array}$$

Glutaric Dialdehyde, pentanedial-1, 5, $OHC(CH_2)_3CHO$, is more readily accessible than succindialdehyde. It is best obtained by hydrolysing the ozonide of *cyclo*pentene (74),

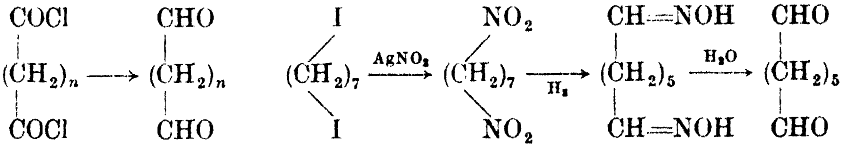


(74)

It is a colourless liquid, b. 188° (70°/10 mm.), which is volatile with steam, and which readily polymerises in the presence of traces of water.

Two simple methods are available for the preparation of dialdehydes of higher carbon content than pentanedial, namely,

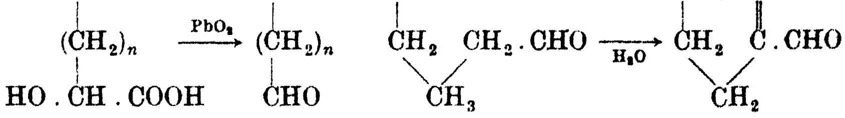
(*a*) Rosenmund's method of reducing the higher di-acid chlorides with hydrogen in the presence of palladium (75).



(75) (76) (77)

(*b*) Braun's method[2] whereby the αω-di-iodo-hydrocarbon (76) is allowed to react with silver nitrite, to give the di-nitroparaffin which is then reduced to the dioxime of the desired dialdehyde (77).

(*c*) The oxidation of a dihydroxy dicarboxylic acid of the type (78), with lead peroxide :—



(78) (79)

Of the higher dialdehydes, adipic dialdehyde, hexanedial, is a valuable substance being converted substantially to *cyclo*pentene aldehyde on heating under pressure with water (79). The main dialdehydes are listed in Table IX.

Few substances containing three aldehyde groups have been prepared, the best known example of the series being mesityl trialdehyde. Aromatic dialdehydes are fairly readily prepared by taking advantage of the fact that when an aromatic hydrocarbon such as *m*-xylene is oxidised with chromic acid the aldehyde is formed as a half-way stage in the oxidation. If the reaction is

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[1] Wohl and Schweitzer, *Ber.*, 1906, **39**, 890.

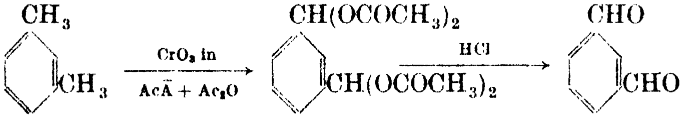
[2] Braun, *ibid.*, 1911, **44**, 2526 ; 1913, **46**, 103.

TABLE IX

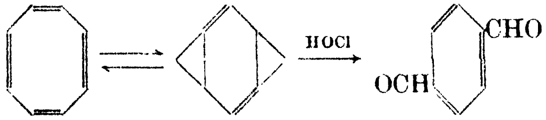
SOME DIALDEHYDES

Systematic name	Structure	B.p.	Usual name, etc.
Ethanedial	$(CHO)_2$	51° (m. 15°)	Glyoxal
Propanedial	$CH_2(CHO)_2$	—	Malondialdehyde
Butanedial	$(CH_2CHO)_2$	67°/13 mm.	Succindialdehyde
Pentanedial	$CH_2(CH_2CHO)_2$	188°	Glutaric dialdehyde
Hexanedial	$(CH_2CH_2CHO)_2$	93°/10 mm.	Adipic dialdehyde
Heptanedial	$CH_2(CH_2CH_2CHO)_2$	111°/33 mm.	Pimelic dialdehyde
Octanedial	$(CH_2CH_2CH_2CHO)_2$	142°/30 mm.	Sebacic dialdehyde
Butene-2-dial	$OHC.CH{=}CH.CHO$	—	Fumaric dialdehyde
Butyne-2-dial	$OHC.C{\equiv}C.CHO$	—	Acetylene dialdehyde (Known only as its tetra-acetal)
		M.p.	
Phthalaldehyde	$C_6H_4(CHO)_2$ (1, 2)	56°	
*iso*Phthalaldehyde	$C_6H_4(CHO)_2$ (1, 3)	89°	
*tere*Phthalaldehyde	$C_6H_4(CHO)_2$ (1, 4)	116°	
Mesityl trialdehyde	$C_6H_3(CHO)_3$ (1, 3, 5)	98°	

carried out in acetic anhydride and acetic acid, to which a little sulphuric acid is added, the tetra-acetate of the dialdehyde is formed, and may be isolated. The dialdehyde is readily obtained by hydrolysis of the tetra-acetate with dilute hydrochloric acid :—



*ere*phthalaldehyde is now obtained in substantial yield from the readily available *cyclo*-octatetrene (80), by oxidation with hypochlorous acid, a duplex extrusion reaction taking place—



(80)

HALOGEN-SUBSTITUTED ALDEHYDES

Liebig, in 1832, discovered [1] chloral, the first halogen-substituted aldehyde to be prepared. Its constitution was elucidated as trichloroacetaldehyde by Dumas two years later.[2] Liebig's method of passing chlorine into alcohol is still, to some extent, used for the preparation of chloral, although more economical methods depending on the direct chlorination of acetaldehyde have been developed.

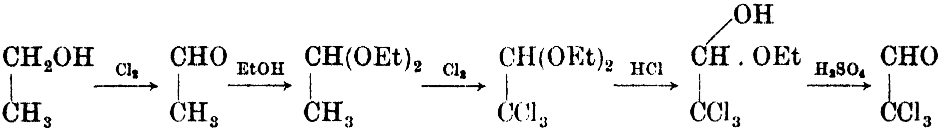
The sequence of reactions by which chloral is obtained from ethanol is obscure, but appears to involve an oxidation to acetaldehyde which, in presence of an excess of alcohol, is immediately converted to the acetal. This is then chlorinated by the further action of the halogen, yielding trichloroacetal or 'chloral diacetal'; that the final product of the reaction is the hemiacetal

---

[1] Liebig, *Ann.*, 1832, **1**, 189.

[2] Dumas, *Ann. Chim. Phys.*, 1834, **56**, 123.

(' chloral alcoholate ') is attributed to partial hydrolysis by the hydrogen chloride formed during the reaction. Industrially the chloral itself is liberated from its ' alcoholate '



$$\begin{matrix}CH_2OH\\|\\CH_3\end{matrix}\xrightarrow{Cl_2}\begin{matrix}CHO\\|\\CH_3\end{matrix}\xrightarrow{EtOH}\begin{matrix}CH(OEt)_2\\|\\CH_3\end{matrix}\xrightarrow{Cl_2}\begin{matrix}CH(OEt)_2\\|\\CCl_3\end{matrix}\xrightarrow{HCl}\begin{matrix}OH\\CH\,.\,OEt\\|\\CCl_3\end{matrix}\xrightarrow{H_2SO_4}\begin{matrix}CHO\\|\\CCl_3\end{matrix}$$

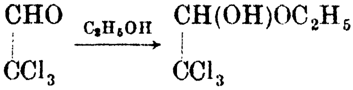
(81)

by stirring with concentrated sulphuric acid. This sequence of reactions is shown in (81). Chloral is a colourless oily liquid b. 97° which has a number of interesting chemical reactions, as well as valuable pharmacological properties. These latter were discovered in 1869 by Liebreich,[1] who observed that the administration of 1 to 5 grams of chloral hydrate induced a peaceful sleep ; it was used in rapidly increasing quantities for this purpose (30,000 lb. in 1873) until the turn of the century when other less nauseating and more powerful sedatives and hypnotics became popular.

Apart from the general reactions of an aldehyde, which it shows normally, chloral has certain unusual reactions which are set out below.

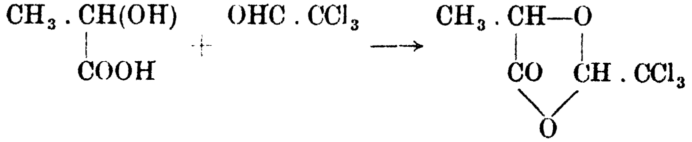
(1) It reacts readily, and exothermically, with water to form a crystalline hydrate, $CCl_3 . CH(OH)_2$, which readily dissolves in water and organic solvents. It has a pungent smell and a sharp taste, m. 57° b. 97° ; the vapour exhibits dissociation and by the use of a good column the hydrate can be separated into its constituents.

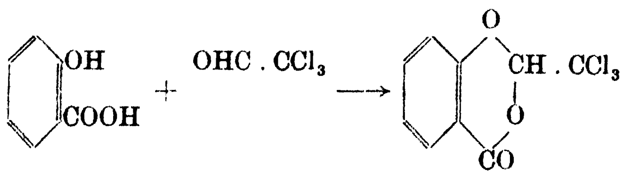
(2) A similar reaction takes place between chloral and alcohols to give the hemiacetal :—



$$\begin{matrix}CHO\\|\\CCl_3\end{matrix}\xrightarrow{C_2H_5OH}\begin{matrix}CH(OH)OC_2H_5\\|\\CCl_3\end{matrix}$$

An extension of this reaction with hydroxy acids leads to cyclic products, the free hydroxyl of the hemiacetal form, yielding an anhydro-link with the carboxyl group. Thus, both lactic and salicylic acid react, thus :—





(3) Heated with caustic alkalies chloral decomposes, giving chloroform and sodium formate :—

$$CCl_3 . CHO + NaOH \longrightarrow CHCl_3 + H . COONa.$$

This is a general reaction which is characteristic of nearly all compounds in which a tertiary carbon atom lies adjacent to a carbonyl group :—

$$(R)_3C . CO . R' + NaOH \longrightarrow (R)_3CH + R'COONa.$$

---

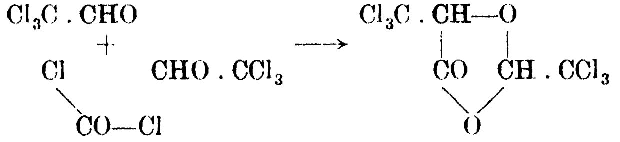
[1] Liebreich, *Ber.*, 1869, **2**, 269.

(4) When chloral hydrate is oxidised with nitric acid it gives trichloracetic acid ;[1] on the other hand, when boiled with aqueous sodium cyanide dichloroacetic acid[2] is formed :—

$$\mathrm{CCl_3 . CH(OH)_2 \xrightarrow{HNO_3} CCl_3\ \ COOH}$$

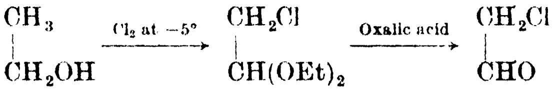
$$\mathrm{CCl_3 . CH(OH)_2 \xrightarrow[-HCN-HCl]{NaCN} CHCl_2 . COONa}$$

(5) Oxidation with oleum converts chloral to chloralide :—



Chloralide

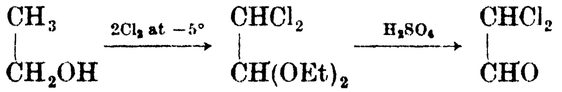
This reaction is probably due to the formation of phosgene by decomposition of part of the chloral. The simple chloroacetaldehyde, $CH_2Cl . CHO$, is more difficult to obtain than is chloral. If paraldehyde is chlorinated and the product treated with alcohol, or if the chlorination of alcohol is controlled by cooling, the diethylacetal of chloroaldehyde (82) is obtained. The aldehyde itself (83) may be obtained from the acetal by heating with crystalline oxalic acid in an inert atmosphere



$$\mathrm{\underset{CH_2OH}{CH_3} \xrightarrow{Cl_2\ at\ -5°} \underset{CH(OEt)_2}{CH_2Cl} \xrightarrow{Oxalic\ acid} \underset{CHO}{CH_2Cl}}$$

(82) (83)

Chloroacetaldehyde is a sharp smelling liquid, b. 85–86°, which forms a crystalline hydrate with water. By carrying the chlorination of alcohol one stage farther dichloroacetal (84) can be obtained, convertible to dichloroacetaldehyde (85), a liquid, which, like other members of this series, yields a crystalline hydrate.



$$\mathrm{\underset{CH_2OH}{CH_3} \xrightarrow{2Cl_2\ at\ -5°} \underset{CH(OEt)_2}{CHCl_2} \xrightarrow{H_2SO_4} \underset{CHO}{CHCl_2}}$$

(84) (85)

The corresponding bromo compounds are :—

	B.P.	*Hydrate.*
Monobromoacetaldehyde	decomp. 80–105°	Leaflets ; m. 51°.
Dibromoacetaldehyde	142°	Prisms ; m. 58–60°.
Tribromoacetaldehyde (Bromal)	174°	Monosymmetric crystals ; m. 53·5°.

Few of the halogen-substituted aromatic aldehydes are commonly encountered ; exceptions are the mono- and dichlorobenzaldehydes used in the production of triphenylmethane dyes. If benzaldehyde is chlorinated with antimony pentachloride in the presence of iodine, a mixture of aldehydes is obtained which yields on distillation three fractions :—

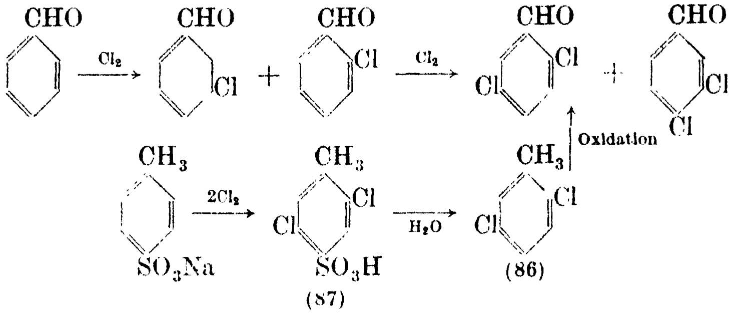
(*a*) *o*- and *m*- monochlorobenzaldehyde (up to 231°).
(*b*) 2, 5-dichlorobenzaldehyde (231–238°).
(*c*) 3, 4-dichlorobenzaldehyde (238–245°).

---

[1] Kolbe, *Ann.*, 1842, **44**, 182.

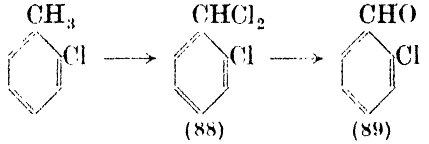
[2] Wallach, *Ber.*, 1877, **10**, 1525

Fraction (*b*) is the largest, only small quantities of the other substances being obtained. 2, 5-Dichlorobenzaldehyde may also be obtained by the oxidation of 2, 5-dichlorotoluene (86) obtained by chlorinating the sodium salt of toluene-*p*-sulphonic acid followed by hydrolysis of the product (87) with superheated steam :—



(87) (86)

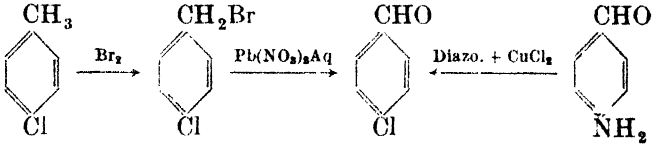
The fore-run of the distillation of the products obtained by the chlorination of benzaldehyde cannot readily be separated into the pure constituents. *o*-Chlorobenzaldehyde (89) is obtained by chlorinating *o*-chlorotoluene to *o*-chlorobenzal chloride (88).



(88) (89)

At the same time some *o*-chlorobenzyl chloride, and some *o*-chlorobenzotrichloride are produced. By stirring the mixture with an excess of 10 per cent. oleum the insoluble *o*-chlorobenzyl chloride rises to the surface as an oil ; the chlorobenzal chloride and chlorobenzotrichloride dissolve and are rapidly hydrolysed to *o*-chlorobenzaldehyde and *o*-chlorobenzoic acid. The upper oily layer is removed and the acid layer poured onto ice when *o*-chlorobenzaldehyde separates as an oil.

The *m*-isomer is best prepared by a cuprous chloride Sandmeyer reaction on *m*-amino-benzaldehyde. The *p*-compound (91) is obtained in like manner from *p*-aminobenzaldehyde, or by brominating *p*-chlorotoluene to give *p*-chlorobenzyl bromide (90) and boiling the latter with aqueous lead nitrate solution :—



(90) (91)

The properties of some of these compounds are shown in Table X.

TABLE X

Substance	*Ortho-*	*Meta-*	*Para-*
Chlorobenzaldehyde	b. 208° (sets at 11°)	b. 210–213°	m. 47·5°
Bromobenzaldehyde	b. 235°	b. 233–236°	m. 57°
Iodobenzaldehyde	—	—	m. 73°
2, 4-Dichlorobenzaldehyde	m.. 58°	—	—

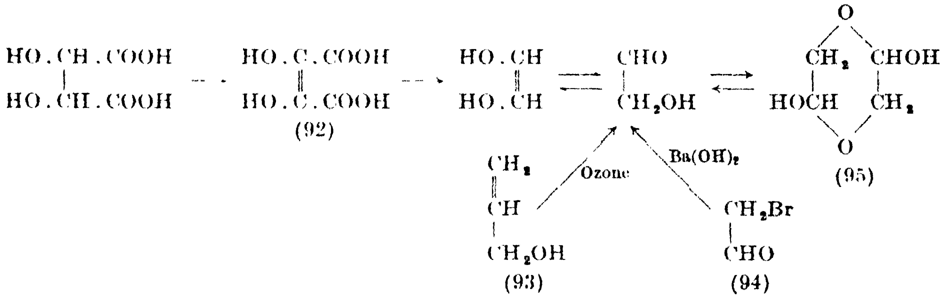
HYDROXYALDEHYDES

The simplest hydroxyaldehyde is glycolaldehyde, $CH_2OH\ .\ CHO$, which may be obtained by a variety of methods. The original method of Fenton and Jackson [1] constitutes a general method by which a 1, 2-glycol,

$$R\ .\ CH(OH)\ .\ CH_2OH$$

can be converted into the hydroxyaldehyde $R\ .\ CH(OH)CHO$. A solution of the glycol is treated with ferrous sulphate and hydrogen peroxide. This reaction still persists even with polyhydroxy compounds such as sorbitol, which may be oxidised to sorbose.

Alternative methods for preparing glycolaldehyde comprise the decarboxylation of dihydroxymaleic acid (92); the oxidation of allyl alcohol (93) and the treatment of monobromoacetaldehyde (94) with baryta. Glycolaldehyde is readily soluble in water, in which it forms a sweet syrup which can be crystallised. The crystals which separate are a dimer, which appears to be 2, 5-dihydroxydioxane (95). On solution in water the monomeric form is regenerated.



Glycolaldehyde exhibits the following reactions :—

(1) With water it forms a stable hydrate.

(2) With traces of alkali its aqueous solution gives an aldol :—

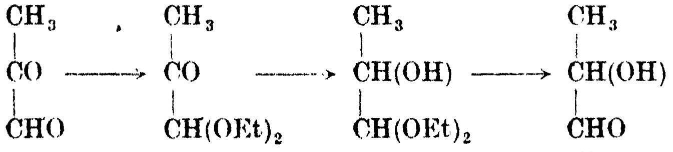
$$CH_2OH\ .\ CHO + CH_2OH\ .\ CHO—CH_2OH\ .\ CHOH\ .\ CHOH\ .\ CHO.$$

(3) Phenylhydrazine forms the osazone of glyoxal, a reaction entirely analogous to the formation of osazones from monose sugars.

(4) It gives the Molisch test—a violet colour with α-naphthol and sulphuric acid.

In general, therefore, glycolaldehyde gives the reactions of a carbohydrate, of which series it is the initial member. The carbohydrates are given special consideration in Chapter VIII.

2-*Hydroxypropanal* (*Lactaldehyde*), $CH_3CH(OH)CHO$, is obtained by reducing the acetal of methylglyoxal (96) with sodium amalgam (97).



$$\begin{array}{ccccccc} CH_3 & & CH_3 & & CH_3 & & CH_3 \\ | & & | & & | & & | \\ CO & \longrightarrow & CO & \longrightarrow & CH(OH) & \longrightarrow & CH(OH) \\ | & & | & & | & & | \\ CHO & & CH(OEt)_2 & & CH(OEt)_2 & & CHO \\ & & (96) & & & & (97) \end{array}$$

Lactaldehyde, which normally exists as the crystalline dimer (98), is readily converted by distillation under normal pressure to acetol (hydroxyacetone) (99), by an isomeric change.

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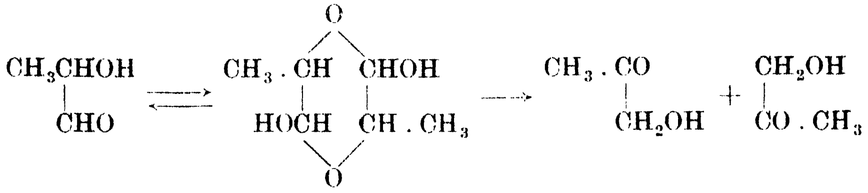
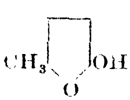
[1] Fenton and Jackson, *J.C.S.*, 1899, **75**, 1.

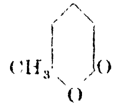


(98) (99)

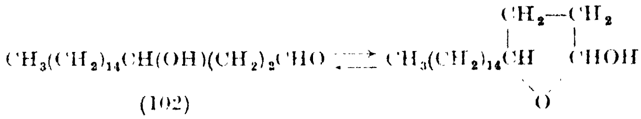
3-Hydroxypropanal (*Hydracrylic aldehyde*), $CH_2OH.CH_2CHO$ is readily prepared by autoclaving an aqueous solution of acrolein. Like its analogues, it forms a dimer readily. As the length of the carbon chain between the hydroxyl and aldehyde group increases, so the tendency to polymer formation decreases, and is replaced by the formation of cyclic hemiacetals, a procedure analogous to lactone formation. Thus, 4-hydroxypentanal (100) and 5-hydroxyhexanol (101) are both isolated as cyclic forms. In the case of



(100)



(101)



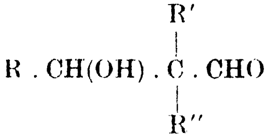
(102) (103)

of 4-hydroxynonadecanal (102) both the open chain and cyclic forms (103) can be isolated, the former having m. 35–40° and the latter m. 64°. The open chain form restores the colour to Schiff's solution, but the cyclic form fails to do so, even on prolonged standing.

Aldols.—All aldols are of necessity hydroxy aldehydes, but are not easily distinguished from members of that group which are not true aldols. The name ' aldol ' took its rise when Würtz [1] condensed two molecules of aldehyde in the presence of hydrochloric acid, so obtaining 3-hydroxybutanal :—

$$CH_3CHO + CH_3CHO \longrightarrow CH_3CH(OH)CH_2CHO$$

which he termed ' aldol ' (from ' *ald*ehyde-alcoh*ol* '). An aldol is, therefore, a hydroxy aldehyde capable of synthesis from two molecules of an aldehyde, or from one molecule each of two aldehydes. Since only the α-hydrogen atom of an aldehyde is capable of entering into such a reaction the structure of aldols is confined to the generic type :—



$$R.CH(OH).\overset{R'}{\underset{R''}{C}}.CHO \qquad CH_2(OH)CH_2CHO$$

(104)

Aldols are, therefore, derivatives of propanol-3-al (104) (see above) which constitutes the initial member of the series, and can be obtained, in poor yield, by the condensation of formaldehyde and acetaldehyde in the presence of a trace of alkali.

Aldol.—The most commonly encountered member, 3-hydroxybutanal, or ' aldol ' itself, is obtained in fair yield by the action of a trace of weak alkali on acetaldehyde, and may be isolated by diluting the reaction mixture with water, and extracting the aldol with ether. Aldol can only be distilled unchanged in vacuum below 80°, since above that temperature it loses water to form acrolein :—

$$\begin{tikzcd} CH_3CH(OH)CH_2CHO \arrow[r, "-H_2O"] \arrow[d] & CH_3CH{=}CHCHO \\ CH_3CHOHCH_2CH_2OH & \end{tikzcd}$$

---

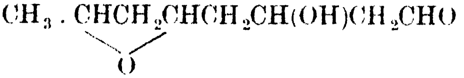
[1] Würtz, *C.R.*, 1872, **74**, 1361 ; 1873, **76**, 1165.

Aldol forms a dimer, on standing, as a crystalline solid (often called "paraldol") (m. 90°); the structure of this dimer is obscure. The reactions of paraldol are interesting; Hibbert[1] showed that on heating with a trace of iodine it is converted almost quantitatively to crotonaldehyde, but if no catalyst is present the reaction takes an entirely different course giving an ester :—

$$CH_3CH(OH)CH_2CO\ .\ O\ .\ CH_2CH_2CH(OH)CH_3$$

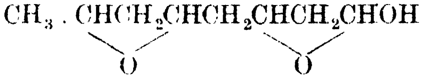
which appears to indicate that 3-hydroxybutyric acid and butane diol-1, 3 are formed by a Cannizzaro reaction and recombine to yield the ester.

Although frequent reference is made in chemical literature to 'aldol' condensations, aldols, even aldol itself, are seldom used in synthetic work. The yield of aldol itself, from aldehyde, is poor and the material is unstable when obtained. The poor yield experienced in the formation of aldol is due, in part, to the formation of a substance, dialdan, $C_8H_{14}O_3$, m. 139°, and its isomer, *iso*-dialdan, m. 118°. Dialdan is an aldehyde, capable of reduction to a glycol, whilst *iso*-dialdan shows neither aldehyde nor unsaturated functions. It is probable that they are represented by the structures (105) and (106) respectively :—



$CH_3\ .\ CHCH_2CHCH_2CH(OH)CH_2CHO$

(105)



$CH_3\ .\ CHCH_2CHCH_2CHCH_2CHOH$

(106)

A few of the more important aldols are listed in Table XI.

TABLE XI

SOME SUBSTITUTED ALDOLS

Name	Formula	Physical properties	Formation
Form*iso*butyraldol	$CH_2(OH)C(CH_3)_2CHO$	m. 90° b. 85° 15 mm.	From HCHO and *iso*-butyraldehyde
Acetpropionaldol	$CH_3CH(OH)CH(CH_3)CHO$	b. 92° 20 mm.	From acetaldehyde and propionaldehyde
Propionaldol	$CH_3CH_2CH(OH)CH(CH_3)CHO$	b. 95° 23 mm.	From two molecules of propionaldehyde
*iso*Butyraldol	$(CH_3)_2CHCH(OH)C(CH_3)_2CHO$	b. 110° 17 mm.	From two molecules of *iso*butyraldehyde
*iso*Butyr-*iso*valer-aldol	$(CH_3)_2CHCH(OH)C(CH_3)\ .\ (C_2H_5)CHO$	b. 95° 23 mm.	From *iso*butyraldehyde and *iso*valeraldehyde

AROMATIC HYDROXYALDEHYDES

About 1834, Pagenstecher, an apothecary of Berne, determined to examine the odorous principle of the meadowsweet and extracted from the flowers of this plant (*Spiræa ulmaria*) what appeared to be an acid oil, giving a purple colour with ferric chloride. Löwig and Weidmann[2] further purified the oil. Piria, in 1839,[3] had discovered an aromatic liquid, which he named 'salicyl hydride', by mild oxidation of the glycoside salicin, and Dumas[4] and Ettling[5] established the identity of the two products. Owing, however, to the acidic nature of the hydroxyl group, the substance was classed as an acid, and was, for some time, known as 'salicylous acid'.

---

[1] Hibbert, *J.A.C.S.*, 1915, **37**, 1748.

[2] Löwig and Weidmann, *Pogg. Ann.*, 1839, **46**, 57.

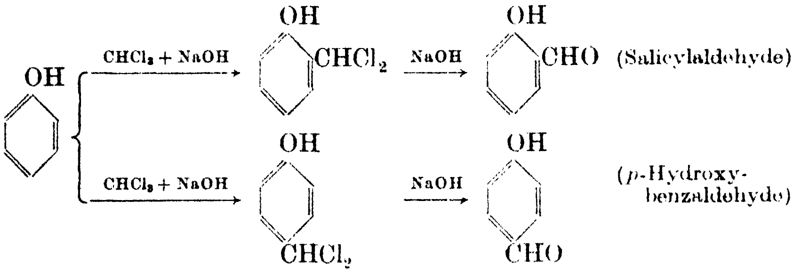
[3] Piria, *Ann.*, 1839, **29**, 300; **30**, 151.

[4] Dumas, *ibid.*, 1839, **29**, 306.

[5] Ettling, *ibid.*, 1839, **29**, 309; 1840, **35**, 241.

The standard method of preparing salicylaldehyde was, for many years, to oxidise salicin with an equal weight of potassium dichromate dissolved in twelve times its weight of 25 per cent. sulphuric acid. On subjecting the mixture to distillation in steam, salicylaldehyde passes over as an oil.

The reaction of Reimer and Tiemann [1] gave a synthetic method of obtaining salicylaldehyde and its analogues by the action of chloroform on an alkaline solution of a phenol. The reaction takes place, presumably, through the intermediate hydroxybenzal chloride :—



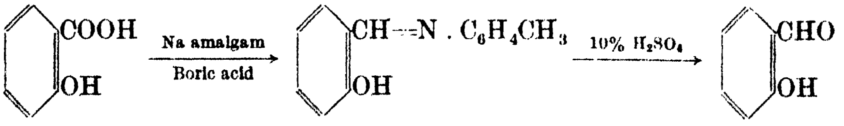
Some *para*hydroxybenzaldehyde is produced at the same time as the salicylaldehyde, but not being volatile with steam does not pass over with the *ortho*-isomer. The yields by the Reimer-Tiemann reaction are very variable—about 20 per cent. of the theoretical quantity of the *ortho*-isomer being obtained. Hodgson and his co-workers [2] have examined the Reimer-Tiemann reaction in some detail, particularly from the standpoint of the relative amounts of *ortho*- and *para*-isomers obtained in the presence of various substituents. Some of their results are summarised in Table XII.

TABLE XII

RATIOS OF *o*-/*p*- ISOMERS PRODUCED IN REIMER-TIEMANN REACTIONS ON PHENOLS $C_6H_4\langle^{R}_{OH}$

R	H	*o*-CH_3	*m*-CH_3	*o*-Cl	*o*-Br	*o*-I	*m*-F	*m*-Cl	*m*-Br	*m*-I	*o*-COOH
o/*p*	0·6	0·48	0·46	1·6	1·25	1·07	0·87	0·71	0·72	0·78	0·06

Fortunately, in order to obtain adequate supplies of salicylaldehyde for synthetic purposes, there is no need to resort to the Reimer-Tiemann reaction; it can be obtained either by reducing salicylic acid in the presence of boric acid and *p*-toluidine :—

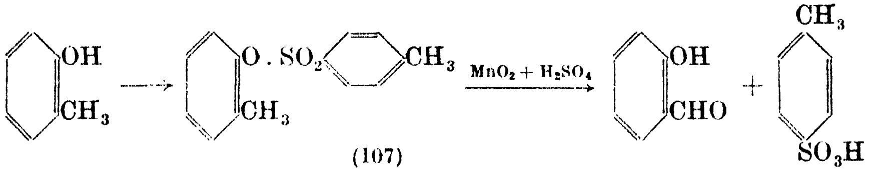


When the condensation product of salicylaldehyde and *para*toluidine separates in good yield; or, as is done industrially, by oxidising a 'protected' ester of *o*-cresol. Usually the protection consists of esterification with *p*-toluene sulphonchloride to give the ester (107) which is oxidised with manganese mud and sulphuric acid to the aldehyde ; this, in turn, is isolated by steaming the reaction mixture :—

---

[1] Reimer and Tiemann, *Ber.*, 1876, **9**, 824.

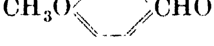
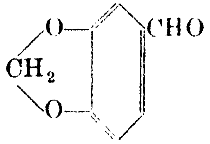
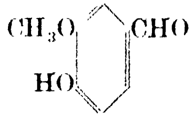
[2] Hodgson and Jenkinson, *J.C.S.*, 1929, 469; 1639; Hodgson and Nixon, *J.C.S.*, 1929, 1632.



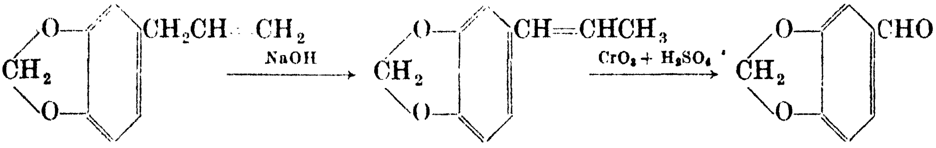
(107)

Salicylaldehyde is an oil, b. 196·5°, which solidifies at low temperatures (m. 20°). Its odour is reminiscent of meadow-sweet ; it gives a violet colouration with ferric chloride.

Many ethers of the hydroxy aromatic aldehydes occur naturally in flowers, fruit and spices and are valued for their pleasant odours. Examples are :—

Anisaldehyde		m. 20° ; b. 248°	Pleasant anise odour.
Piperonal		m. 36° ; b. 263°	Has a pleasant odour of heliotrope, and is mainly used for flavouring custard-powder.
Vanillin		m. 80° ; b. 170°/15 mm.	The odorous principle of the vanilla-pod.

The production of piperonal and vanillin on an industrial scale are important manufacturing operations. Piperonal is readily made by converting safrole

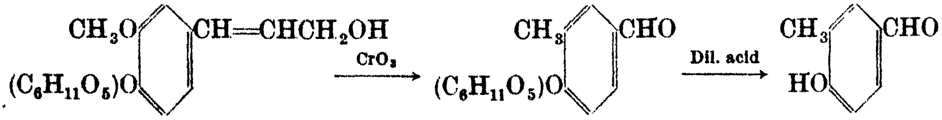


(108) (109) (110)

(108) to *iso*-safrole (109) by heating with alkali (allylic rearrangement) ; *iso*-safrole is readily oxidised to piperonal (110) by chromic acid, or by manganese mud and sulphuric acid. As safrole is readily obtainable, being the major constituent of the essential oil of sassafras, this procedure serves to provide the piperonal required by industry.

Considerable ingenuity has been expended on devising methods for obtaining vanillin, which is, without doubt, the most widely used flavouring agent. Vanillin is very widely distributed in nature ; apart from its well-known occurrence in the vanilla-pod (*V. planifolia*) vanillin is found in *Scorzonera* flowers, in *Lupinus albus*, many orchids and in a host of other plants ; as its glycoside it is often met with as a crystalline efflorescence on the sunny side of beech-trees.

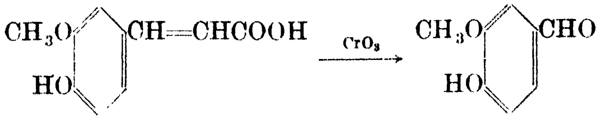
The earliest chemical preparations of vanillin were from coniferin (111), a glucoside of coniferyl alcohol which is distributed throughout the cambial sap



(111) (112) (113)

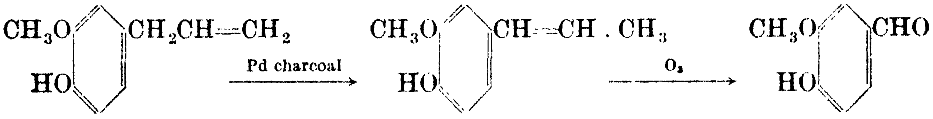
of all coniferous trees. When oxidised with dilute acid and sodium dichromate, vanillin (113) is obtained, glucovanillin (112) being formed as an intermediate.

By a similar oxidation vanillin may be obtained from ferulic acid (113a) obtainable in large quantities from ferula and black fir resins :—



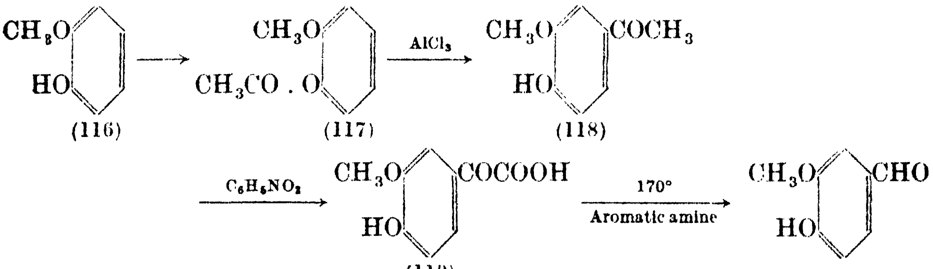
(113a)

Until recently the most practicable method of preparing vanillin in bulk has been by isolating eugenol (114) from cloves (*Eugenia caryophyllata*) and isomerising this to *iso*-eugenol (115) ; older methods recommend potash for this conversion, but palladised charcoal is equally effective and much easier to separate from the product. To oxidise *iso*-eugenol to vanillin, the former is churned into an emulsion with water and treated at a low temperature with ozonised air :—



(114) (115)

Many attempts have been made to use guaiacol (116) as a starting point for the industrial production of vanillin ; several apparently successful methods have been worked out, e.g. :—



(116) (117) (118) (119)

in which guaiacol acetate (117) is heated with anhydrous aluminium chloride, giving the isomeric ketone (118). By oxidising the latter compound with nitrobenzene, vanilloyl formic acid (119) is obtained, which can be decarboxylated to vanillin by heating to 170° in the presence of a tertiary aromatic amine.

The main trouble with all processes commencing with guaiacol is that the product has a persistent ' off-flavour ' due to the obstinate adherence of traces of raw material to the finished products. Recently, vanillin of excellent quality and in enormous quantity has been obtained by treating the waste sulphite liquors from the paper-pulp industry. The process of ' sulphiting ', to remove lignins from the paper-stock, involves conversion of the lignins to a soluble product, the cellulose remaining unchanged. The occurrence in lignin (*q.v.*) of a potential vanillin structure leads to its release when the spent sulphite lye is diluted and autoclaved.

KETONES

The early history of the ketone family has been touched upon in the introduction to this chapter. As soon as Williamson had established the structure of acetone, the discovery and recognition of other ketones followed rapidly, as, for example, the discovery by Wanklyn[1] that diethylketone can be obtained by the action of carbon monoxide on sodium ethyl.

---

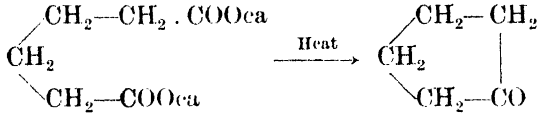
[1] Wanklyn, *Phil. Mag.*, 1866 [4], **31**, 505.

The main methods by which ketones may be prepared are set out below :—

(1) *Action of Heat on Salts of Carboxylic Acids.*—Since acetone was first prepared by the action of heat on calcium acetate, the reaction :—

$$2R\,.\,COOca\,{*} \longrightarrow R\,.\,CO\,.\,R + CaCO_3$$

has proved a valuable standard method. In many cases the yields are low, but may be improved by using the barium or thorium salts. Thus, in producing *cyclo*pentanone the method of heating the barium salt of adipic acid (120)



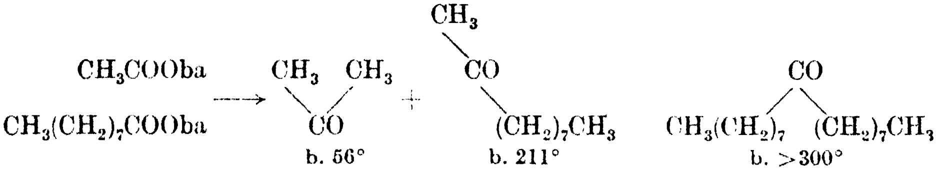
(120)

gives a yield of over 70 per cent. Ruzicka, in his researches on the higher cyclic ketones (see Appendix II) found that the thorium salts give the highest yield.

Mixed ketones can be obtained by heating intimate mixtures of the calcium salts of two acids :—

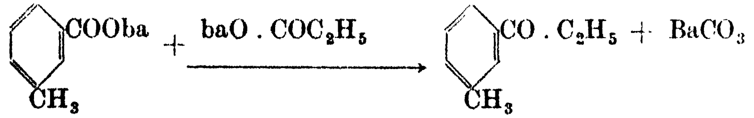
$$R\,.\,COOca + R'\,.\,COOca \longrightarrow R\,.\,CO\,.\,R' + CaCO_3.$$

The reaction cannot, of course, be restrained from giving substantial amounts of the two ketones R . CO . R and R' . CO . R', which necessitates a careful fractional distillation to separate the three products. The reaction is most successful when there is a considerable disparity between the size of R and R'. Thus, when barium pelargonate and acetate are distilled together, the three ketones, acetone, decanone-2 and heptadecanone-8 are obtained :—



These are easily separated by distillation ; as the main objective in such a reaction must be the decanone-2, the yield may be increased by using a large excess of the relatively cheap barium acetate ; this increases the amount of acetone formed, but decreases the yield of heptadecanone-8, thereby raising the efficiency of conversion of barium pelargonate to decanone-2.

Although the calcium or barium salt method is often described as obsolete for practical purposes, this is far from being the case, as it affords the only practical method of approach to the *o*- and *m*-alkyl substituted derivatives of acetophenone and its homologues. Thus, to prepare *m*-tolyl ethyl ketone (121), the Friedel Crafts reaction is inadmissible (giving the *p*-derivative) ; other methods—*m*-toluic nitrile and ethyl magnesium iodide, for example—are expensive and give surprisingly small yields ; easily the most practicable method of obtaining the ketone is to distil a mixture of barium-*m*-toluate and barium propionate, when yields up to 28 per cent. of the desired ketone are obtained :—



(121)

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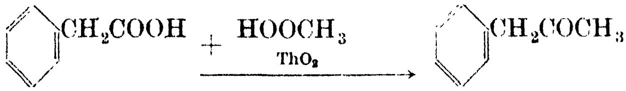
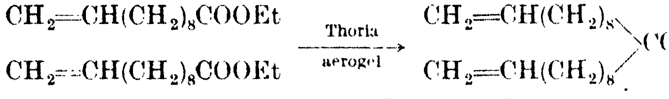
* 'ca' is used throughout this section to indicate the calcium salt of the acid and to avoid unnecessary duplication of formulæ.

Attempts have been made to convert the calcium salt method to a continuous process by the passage of the vapours of an acid over a catalyst—thorium oxide proving the most successful.[1] The reaction appears to be most successful when a aralkyl and a simple alkyl acid are used together. Thus phenyl acetone [2] may be obtained :—



Swann, Appel and Kistler [3] showed that the catalytic method is more successful for ketones of higher molecular weights when the esters of the acids are passed over the catalyst. Thus, comparatively complex ketones such as laurone, stearone and undecylenone can be obtained simply and in good yield from ethyl laurate, stearate or undecylenate, e.g.,



$$\begin{array}{l} CH_2{=}CH(CH_2)_8COOEt \\ CH_2{=}CH(CH_2)_8COOEt \end{array} \xrightarrow[\text{aerogel}]{\text{Thoria}} \begin{array}{l} CH_2{=}CH(CH_2)_8\diagdown \\ \qquad\qquad\qquad\qquad CO \\ CH_2{=}CH(CH_2)_8\diagup \end{array}$$

(2) *Methods Depending on the Grignard Reagent.*—It is customary to regard the intermediate stage in the action of a Grignard reagent upon an ester, as being the formation of the ketone :—

$$R\,.\,COOEt + MgR'Br \longrightarrow R\,.\,CO\,.\,R' + MgR'Br \longrightarrow R\,.\,C(OH)(R')_2.$$

but it is almost impossible to isolate the ketone, further reaction to the tertiary alcohol stage being preponderant. The work of Kohler *et al.*,[4] has shown that the ketone formation is more easily controlled with unsaturated esters, as in the formation of

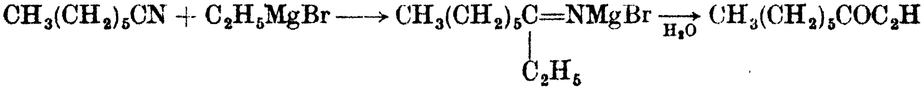
$$CH_3CH_2CH{=}CHCOOEt + C_2H_5MgI \longrightarrow \underset{(122)}{CH_3CH_2CH{=}CH\,.\,COC_2H_5}$$

4-heptenone-3 (122).

If, in this reaction, the ester is replaced by the acid chloride, the reaction is much more satisfactory, always provided that, as shown by Gilman and Mayhue [5] the Grignard solution is added to the acid chloride, and not *vice versa.* The method has been developed by Fordyce and Johnson [6] for obtaining long-chain ketonic acids, as in :—

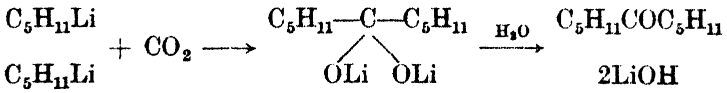
$$\begin{array}{c} (CH_3)_2CH(CH_2)_3MgBr + ClCO(CH_2)_8COCl \\ \downarrow \\ (CH_3)_2CH(CH_2)_3CO(CH_2)_8COOH \end{array}$$

10-keto *iso*palmitic acid. A further extension of the reaction is the action of Grignard reagents on nitriles containing the group —CH_2CN, which react :—



$$CH_3(CH_2)_5CN + C_2H_5MgBr \longrightarrow CH_3(CH_2)_5\underset{\displaystyle C_2H_5}{\underset{|}{C}}{=}NMgBr \xrightarrow[H_2O]{} CH_3(CH_2)_5COC_2H_5.$$

(3) *The Use of Other Organo-Metallic Compounds.*—When carbon dioxide is bubbled through a solution or suspension of a lithium alkyl or aryl, a complex is formed, which on decomposition forms the ketone :—



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[1] Pickard and Kenyon, *J.C.S.*, 1911, **99**, 57.
[2] Organic Synthesis, 1943, *Coll. 2*, 389.
[3] Swann, Appel and Kistler, *Ind. Eng. Chem.*, 1934, **26**, 388, 1014.
[4] Kohler *et al.*, *Ann. Chem. J.*, 1905, **33**, 21,153 ; *ibid.* 1905, **34**, 132.
[5] Gilman and Mayhue, *Rec. Trav. Chim.*, 1932, **51**, 47.
[6] Fordyce and Johnson, *J.A.C.S.*, 1933, **55**, 3368.

(4) *Oxidation of Secondary Alcohols.*—Secondary alcohols are readily oxidised by chromic acid, by manganese mud and sulphuric acid, or catalytically, thus :—

$$RCH(OH)R' \xrightarrow{-H_2} RCOR'$$

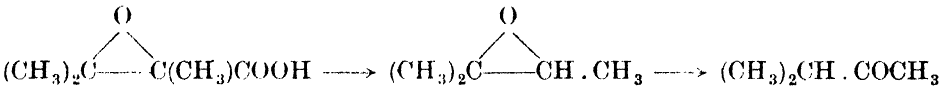
a process which constitutes a satisfactory approach to many unsymmetrical ketones.

(5) *The Pinacol-Pinacone Transformation.*—This reaction depends on the tendency which a tetra-substituted ethylene glycol shows towards loss of water and the formation of a ketone, according to the plan :—

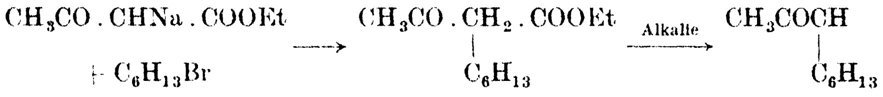
$$\underset{\text{Pinacol}}{(CH_3)_2C(OH)\,.\,C(OH)(CH_3)_2} \xrightarrow{H_2O} \underset{\text{Pinacone}}{(CH_3)_3C\,.\,COCH_3}$$

It will be noted, in passing, that a complex rearrangement has taken place, and that the generic terms "pinacol" and "pinacone" are used to refer to the glycol and ketone forms respectively (in preference to the older "pinacoline-pinacolone"). Although the reaction is a general one, it is somewhat restricted by the limited availability of the starting materials.

(6) The thermal decomposition of glycidic acids is also capable of giving ketones, and is related to the pinacol-pinacone transformation :—



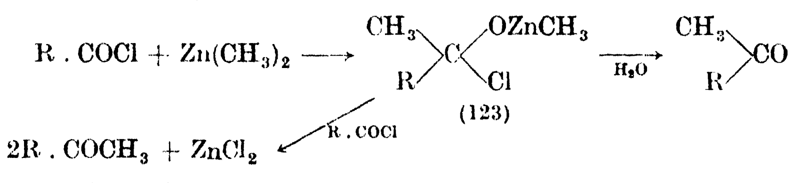
(7) The alkaline hydrolysis of acetoacetic ester and of its alkyl derivatives is also a prolific source of ketones, and by using other ketonic esters the range can be extended :—



$$\begin{matrix} CH_3CO\,.\,CHNa\,.\,COOEt \\ +\ C_6H_{13}Br \end{matrix} \longrightarrow \begin{matrix} CH_3CO\,.\,CH_2\,.\,COOEt \\ | \\ C_6H_{13} \end{matrix} \xrightarrow{\text{Alkali}} \begin{matrix} CH_3COCH \\ | \\ C_6H_{13} \end{matrix}$$

Nonanone-2

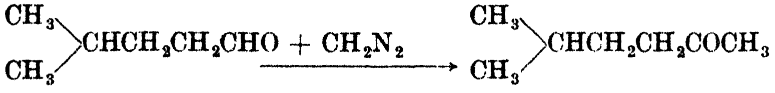
(8) *Zinc-alkyl methods of Ketone Synthesis.*—Whilst methods using zinc-alkyls are to be avoided, if possible, the reaction of these substances with acid chlorides gives a good yield of ketone :—



(123)

The first product of reaction (123), could be decomposed with water to give the ketone, but the addition of a further quantity of the acid chloride leads to decomposition along more economic lines, with the formation of an additional quantity of the ketone. The method also works with long chain diacid chlorides, leading to the long-chain diketones.

(9) *Direct Alkylation of Aldehydes.*—This can be carried out by the use of diazomethane, thus :—

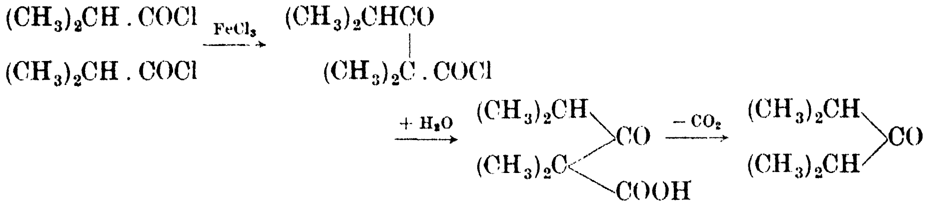


$$(CH_3)_2CHCH_2CH_2CHO + CH_2N_2 \longrightarrow (CH_3)_2CHCH_2CH_2COCH_3$$

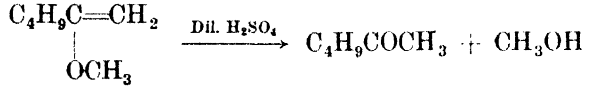
The method is limited by the fact that only ketones in which one unit is the methyl group can be obtained.

(10) Friedel-Crafts methods are described in an Appendix to Chapter III.

(11) Anhydrous ferric chloride will convert an acid chloride to the corresponding ketone by the sequence of reactions set out below :—

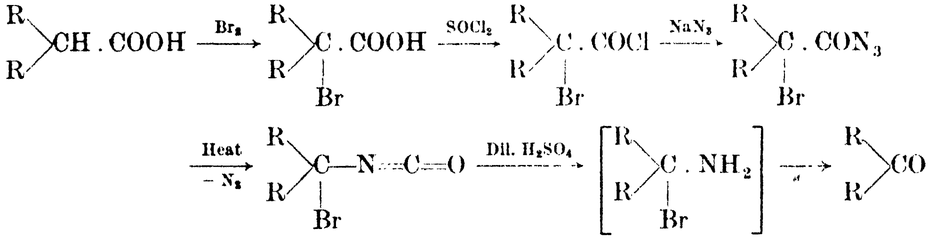


(12) Ketones can be obtained by the decomposition of unsaturated ethers containing an $\alpha\beta$-configuration, thus :—



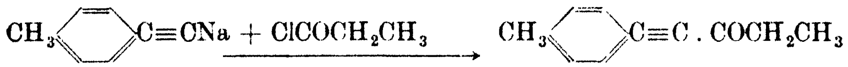
$$\underset{\displaystyle OCH_3}{C_4H_9C{=}CH_2} \xrightarrow{\text{Dil. } H_2SO_4} C_4H_9COCH_3 + CH_3OH$$

(13) The method developed by Braun[1] is not available except in rare cases for preparative work, but is useful in establishing constitution :—



The stages set out above are sufficient to indicate the course of the reactions.

(14) Special mention must be made of the method of building up ketones by the action of an acid chloride on a sodium acetylide ; thus, when the sodium derivative of *p*-tolylacetylene (12) reacts with propionyl chloride, *p*-tolylpentyne-one-3 (125) is obtained.



(124) (125)

SOME INDIVIDUAL KETONES

The physical properties of some of the aliphatic ketones are shown in Table XIII from which it will be seen that the common nomenclature is somewhat confused.

Acetone, CH_3COCH_3.—Reference has been made, in the introduction to this chapter, to the original observations of Libavius on the distillation of sugar of lead in which a peculiar combustible liquid or " quintessence " was formed. The true composition of acetone was elucidated by Liebig[2] and by Dumas,[3] but they did not indicate its structure ; this was done by Williamson, who regarded acetone as ' methyl acetyl '—or acetyl hydride (ethanal) in which the hydride hydrogen had been replaced by methyl. When Freund[4] carried out the synthesis suggested by Chiozza,[5] the action of zinc methyl on acetyl chloride, acetone was prepared for the first time by a method indicating its structure.

---

[1] Braun, *Ber.*, 1931, **64**, 2866 ; 1934, **67**, 218.

[2] Liebig, *Ann.*, 1832, **1**, 223.

[3] Dumas, *Ann. Chrim. Phys.*, 1831 [2], **47**, 203.

[4] Freund, *ibid.*, 1861, **118**, 1.

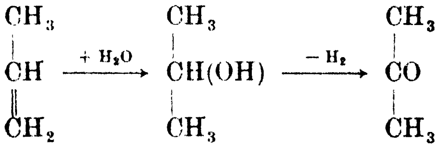
[5] Chiozza, *Ann.*, 1853, **85**, 232.

The first industrial production of acetone was by the fractionation of the forerun of the redistillation of crude wood spirit, from the destructive distillation of wood ; although contaminated with methanol, an acetone of 92 per cent. strength can be obtained in this way. As the demand for acetone grew, more and more acetone was prepared from the destructive distillation of the 'grey acetate ', obtained by neutralising the acid part of the pyroligneous liquor with lime.

These methods sufficed to supply acetone until the first Great War, when cellulose acetate 'dopes' were used for the first time, and acetone was in considerable demand as a solvent. As soon as acetic acid was available from acetylene, the sequence of reactions shown below was used to obtain acetone :—

$$CH{\equiv}CH \xrightarrow{H_2O} CH_3CHO \xrightarrow{\text{Oxidation}} CH_3COOH \xrightarrow{CaO} (CH_3COO)Ca$$
$$\xrightarrow{\text{Heat}} CH_3COCH_3 + CaCO_3$$

The conversion of the acid was soon carried out catalytically, the vapour being passed over lime, alumina or thoria ; excellent yields are also obtained with iron filings at 600°. The cost was high, and in order to supplement the amounts available, recourse was taken to fermentation processes in which maize-mash or molasses is fermented with special organisms, acetone and butanol being obtained in proportions approximately 2 : 1. At the time when this process was first introduced, acetone was the substance of primary interest, and the butanol was regarded as an undesirable by-product. To-day, the reverse is true ; the numerous uses which have been found for butanol and its esters make the process valuable for the production of butanol, the acetone being regarded as a by-product. Cracker gas can be made to give propylene and the sequence of reactions :—



$$\begin{matrix} CH_3 \\ | \\ CH \\ \| \\ CH_2 \end{matrix} \xrightarrow{+H_2O} \begin{matrix} CH_3 \\ | \\ CH(OH) \\ | \\ CH_3 \end{matrix} \xrightarrow{-H_2} \begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{matrix}$$

can be carried out at considerably lower cost than that of fermentation of maize or molasses. Where cracker gas is not available the most promising method of production appears to be the peculiar reaction which acetylene undergoes when passed with steam over a zinc-oxide mass catalyst at 400°.

$$2C_2H_2 + 3H_2O \longrightarrow CH_3COCH_3 + CO_2 + 2H_2.$$

Although mention is often made of the occurrence of acetone in the urine of diabetic patients, it must be recalled that acetone, in small quantities is a normal constituent of both blood and urine, and also of many plant fluids.

Acetone is a colourless liquid, of characteristic but not unpleasant smell, and is miscible with water in all proportions. It is an excellent solvent for a vast range of organic compounds, and, in addition, dissolves many inorganic salts, of which potassium iodide and permanganate are of interest to the organic chemist.

Vigorous reduction of acetone by Clemmensen's method gives a moderate yield of the hydrocarbon ; the catalytic methods yield *iso*-propyl alcohol. This method was, at one time, an important method by which *iso*-propyl alcohol was obtained industrially, but the separation of large quantities of propylene from cracker gas has reversed the position.

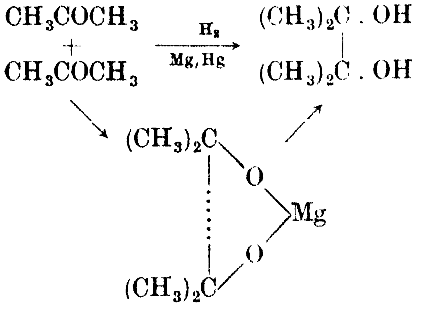
TABLE XIII

SOME ALIPHATIC KETONES

Systematic name	Formula	M.P.	B.P.	Common name
Propanone-2	CH_3COCH_3	— 94°	56·5°	Acetone
Butanone-2	$CH_3CH_2COCH_3$	—	81°	Methyl ethylketone
Pentanone-2	$CH_3CH_2CH_2COCH_3$	—	102°	Methyl propylketone
Pentanone-3	$CH_3CH_2COCH_2CH_3$	— 41·5°	103°	Propione Di-*n*-propylketone
Hexanone-2	$CH_3(CH_2)_3COCH_3$	—	127°	β-Oxo-hexane *n*-Valeryl methyl ketone Methylbutylketone
Hexanone-3	$CH_3(CH_2)_2COCH_2CH_3$	—	123°	γ-Oxohexane Ethyl propylketone
Heptanone-4	$CH_3(CH_2)_2CO(CH_2)_2CH_3$	— 34°	144°	Butyrone
Octanone-2	$CH_3(CH_2)_5COCH_3$	—	171°	Methylœnanthone Methylhexylketone
Nonanone-2	$CH_3(CH_2)_6COCH_3$	— 15°	193°	Methylheptylketone
Nonanone-5	$CH_3(CH_2)_3CO(CH_2)_3CH_3$	— 6°	187°	Valerone Di-*n*-butyl ketone
Decanone-2	$CH_3(CH_2)_7COCH_3$	+ 3·5°	211°	Methyl-*n*-octylketone
Undecanone-2	$CH_3(CH_2)_8COCH_3$	+ 15°	225°	Methyl-nonyl ketone
Undecanone-6	$CH_3(CH_2)_4CO(CH_2)_4CH_3$	15°	226°	Caprone Di-*n*-amyl ketone
Dodecanone-2	$CH_3(CH_2)_9COCH_3$	21°	247°	Methyl-decyl ketone
Tridecanone-2	$CH_3(CH_2)_{10}COCH_3$	28°	263°	Methyl undecylketone
Tridecanone-7	$CH_3(CH_2)_5CO(CH_2)_5CH_3$	30°	264°	Œnanthone Di-*n*-hexylketone
Tetradecanone-2	$CH_3(CH_2)_{11}COCH_3$	34°	207°/100 mm.	Methyldodecylketone
Pentadecanone-2	$CH_3(CH_2)_{12}COCH_3$	39°	224°/100 mm.	Methyltridecylketone
Pentadecanone-8	$CH_3(CH_2)_6CO(CH_2)_6CH_3$	40°	—	Caprylone
Hexadecanone-2	$CH_3(CH_2)_{13}COCH_3$	43°	231°/100 mm.	
Heptadecanone-2	$CH_3(CH_2)_{14}COCH_3$	48°	244°/100 mm.	
Heptadecanone-9	$CH_3(CH_2)_7CO(CH_2)_7CH_3$	50°	—	Pelargone Caprinone

Octadecanone-2	$CH_3(CH_2)_{15}COCH_3$	52°	252°/100 mm.	
Nonadecanone-2	$CH_3(CH_2)_{16}COCH_3$	55°	265°/100 mm.	
Tricosanone-12	$CH_3(CH_2)_{10}CO(CH_2)_{10}CH_3$	69°	—	Laurone
Heptacosanone-14	$CH_3(CH_2)_{12}CO(CH_2)_{12}CH_3$	76°	—	Myristone
Hentriacontanone-16	$CH_3(CH_2)_{14}CO(CH_2)_{14}CH_3$	83°	—	Palmitone
Pentatriacontanone-18	$CH_3(CH_2)_{16}CO(CH_2)_{16}CH_3$	88°	—	Stearone
2-Methylbutanone-3	$(CH_3)_2CHCOCH_3$	—	96°	Methyl *iso*-propylketone
2, 2-Dimethylbutanone-3	$(CH_3)_3C \, . \, COCH_3$	—	106°	Methyl *ter*-butylketone
3, 3-Dimethylpentanone-2	$CH_3CH_2C(CH_3)_2COCH_3$	—	131°	Methyl *ter*-amylketone
2, 4-Dimethylpentanone-3	$(CH_3)_2CHCOCH(CH_3)_2$	—	125°	Tetramethylacetone
2, 2, 4-Trimethylpentanone-3	$(CH_3)_3C \, . \, COCH(CH_3)_2$	—	134°	Pentamethylacetone
2, 2, 4, 4-Tetramethylpentanone-3	$(CH_3)_3C \, . \, CO \, . \, C(CH_3)_3$	—	150°	Pivalone Hexamethylacetone
Butenone	$CH_2{=}CHCOCH_3$	—	80°	Vinylmethylketone
2-Methylbutenone	$CH_2{=}C(CH_3)COCH_3$	—	96°	*iso*-Propenylmethylketone
Pentenone-3	$CH_2{=}CHCOCH_2CH_3$	—	32°/50 mm.	Vinylethylketone
Pentenone-4	$CH_2{=}CHCH_2COCH_3$	—	108°	Allymethylketone
2-Pentenone-4	$CH_3CH{=}CHCOCH_3$	—	122°	Ethylidene acetone
2-Methyl-2-pentenone-4	$(CH_3)_2C{=}CHCOCH_3$	—	130°	Mesityl oxide
Hexenone-3	$CH_2{=}CHCOCH_2CH_2CH_3$	—	24°/10 mm.	Vinylpropylketone
Hexenone-4	$CH_2{=}CHCH_2COCH_2CH_3$	—	127°	Allylethylketone
2-Hexenone-4	$CH_3CH{=}CHCOCH_2CH_3$	—	137°	Propenylethylketone
2-Hexenone-5	$CH_3CH{=}CHCH_2COCH_3$	—	—	Allylacetone
5-Methylhexenone-3	$CH_2{=}CHCOCH_2CH(CH_3)_2$	—	32°/10 mm.	Vinyl*iso*butylketone
Heptenone-4	$CH_2{=}CHCH_2COCH_2CH_2CH_3$	—	147°	Allylpropylketone
2-Heptenone-4	$CH_3CH{=}CHCOCH_2CH_2CH_3$	—	157°	Propenylpropylketone
2, 4-Heptadienone-6	$CH_3CH{=}CHCH{=}CHCOCH_3$	—	79°/16 mm.	—
2-Methyl-2-heptenone-6	$(CH_3)_2C{=}CHCH_2CH_2COCH_3$	—	173°	Methyheptenone
2, 6-Dimethyl-2, 5-heptadienone-4	$(CH_3)_2C{=}CHCOCH{=}C(CH_3)_2$	28°	196°	Phorone
5-Methyl-3-heptenone-2	$(CH_3)_2CHCH_2CH{=}CHCOCH_3$	—	180°	*iso*-Amylideneacetone
2, 4-Octadienone-6	$CH_3(CH{=}CH)_2COCH_2CH_3$	—	93°/26 mm.	—
1, 8-Nonadienone-5	$CH_2{=}CH(CH_2)_2CO(CH_2)_2CH{=}CH_2$	—	117°/60 mm.	Diallyl acetone
2-Pentynone-4	$CH_3C{\equiv}C \, . \, COCH_3$	—	133°	Methyl α-propynyl ketone
3-Nonynone-2	$CH_3(CH_2)_4C{\equiv}C \, . \, COCH_3$	—	84°/12 mm.	Acetylœnanthylidene

Nearly all reductions of acetone yield a little pinacol (126), and the use of magnesium activated by mercury under the conditions laid down by Holleman[1] enables pinacol to be obtained in substantial yield



(126)

(127)

Couturier and Meunier[2] have shown that a magnesium derivative of pinacol is formed during this reaction and postulate the formation through the intermediate (127).

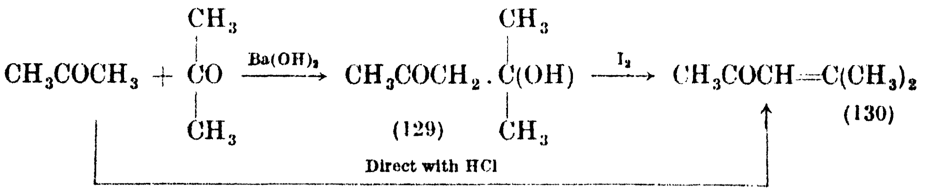
The most interesting oxidation of acetone is that by which it is converted by selenium dioxide to pyruvic aldehyde (128) :—

$$\underset{}{CH_3COCH_3} \longrightarrow \underset{(128)}{CH_3COCHO} \qquad \underset{(128a)}{CHO\,.\,CO\,.\,CHO}$$

This process cannot, apparently, be carried further, to produce mesoxalic dialdehyde (128*a*). If acetone (which, in general, is not easily oxidised) is submitted to the action of very powerful oxidising agents the chain is destroyed and only carbon dioxide with traces of acetic acid can be isolated.

The decomposition of acetone by heat, to give keten is discussed in Chapter VII, and it is only necessary here to remark on the absence of any tendency on the part of ketones to polymerise in the ordinary sense.

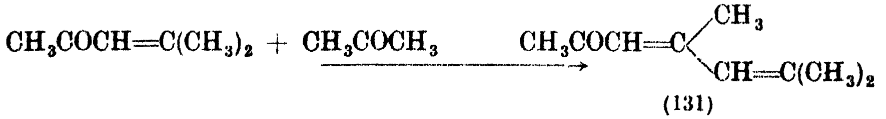
On the other hand, ketones readily enter into condensation reactions of the aldol type. Thus, acetone gives diacetone alcohol (2-methylpentanol-2, one-4) (129) on treatment with solid baryta :—



$$CH_3COCH_3 + \overset{CH_3}{\underset{CH_3}{CO}} \xrightarrow{Ba(OH)_2} \underset{(129)}{CH_3COCH_2\,.\,\overset{CH_3}{\underset{CH_3}{C(OH)}}} \xrightarrow{I_2} \underset{(130)}{CH_3COCH{=}C(CH_3)_2}$$

Direct with HCl

Diacetone alcohol is a valuable intermediate yielding important bases on reaction with ammonia ; it is dehydrated by boiling in the presence of iodine, to mesityl oxide (130), an unsaturated ketone. Mesityl oxide (2-methylpentene-2, one-4) can be obtained direct from acetone by the action of hydrogen chloride, and still retains its ability to condense with a further molecule of acetone to give phorone (131) :—



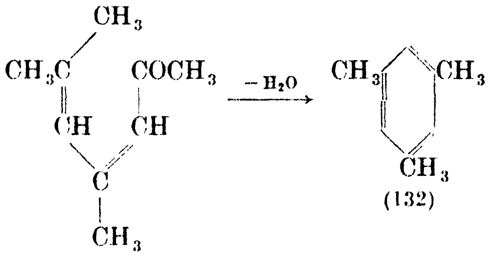
$$CH_3COCH{=}C(CH_3)_2 + CH_3COCH_3 \longrightarrow \underset{(131)}{CH_3COCH{=}C\begin{cases}CH_3\\CH{=}C(CH_3)_2\end{cases}}$$

---

[1] Holleman, *Rev. Trav. Chim.*, 1906, **25**, 206.

[2] Couturier and Meunier, *C.R.* 1905, **140**, 721.

Finally, if the condensation of acetone to these unsaturated ketones be attempted in the presence of concentrated sulphuric acid, the main product is mesitylene (132) :—



(132)

It must, however, be pointed out that when mesityl oxide and acetone react phorone is not the only product, since the methyl group adjacent to the keto group of mesityl oxide can also react to give an isomer of phorone :—

$$CH_3COCH_3 + CH_3COCH{=}C(CH_3)_2 \longrightarrow \underset{(133)}{(CH_3)_2C{=}CH\,.\,CO\,.\,CH{=}C(CH_3)_2}$$

This isomer (133), does not give mesitylene on further condensation. In addition, phorone can react with more acetone, thus :—

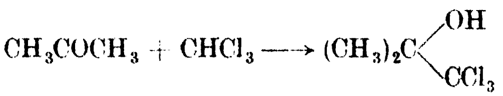
$$\begin{array}{r}CH_3COCH_3 + CH_3COCH{=}C(CH_3)CH{=}C(CH_3)_2 \;\bigg\downarrow \\ (CH_3)_2C{=}CH\,.\,CO\,.\,CH{=}C(CH_3)CH{=}C(CH_3)_2\end{array}$$

Since, in the condensation of acetone in the presence of sulphuric acid, all thsee reactions proceed simultaneously the final product is very complex, and seldom contains more than 20–25 per cent. of mesitylene.

There are two 'condensation' reactions given by acetone which are of considerable interest, and which throw some light on the lability of the hydrogen atoms of this ketone. If acetone is allowed to stand with formaldehyde and dimethylamine, a reaction takes place in which up to six hydrogen atoms are replaced :—

$$\begin{array}{l}CH_3COCH_3 + HCHO + NH(CH_3)_2 \longrightarrow CH_3COCH_2CH_2N(CH_3)_2 \\ \quad\longrightarrow CH_3COCH[CH_2N(CH_3)_2]_2 \longrightarrow [(CH_3)_2NCH_2]_3C\,.\,CO\,.\,C[CH_2N(CH_3)_2]_3\end{array}$$

The second reaction is that with chloroform :—



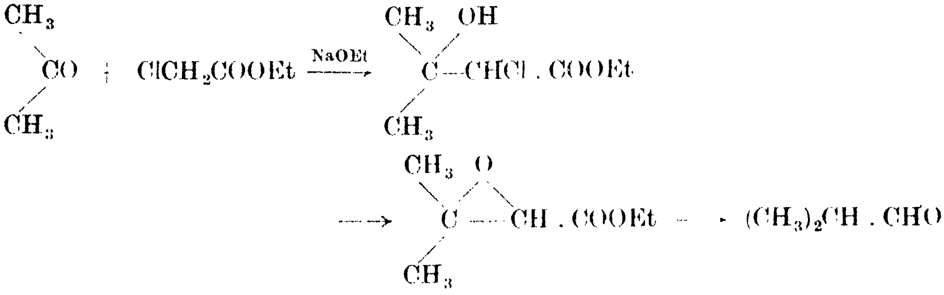
$$CH_3COCH_3 + CHCl_3 \longrightarrow (CH_3)_2C\begin{cases}OH\\CCl_3\end{cases}$$

giving ααα-trichloro-*ter*-butyl alcohol ('*Chloretone*').

The reactions of acetone with esters is complex, and even with sodium ethylate present does not always take the typical 'Claisen reaction' course. Thus, with ethyl acetate and sodium ethylate the normal reaction yielding 2, 4-pentanedione (acetylacetone) ensues :—

$$CH_3COCH_3 + CH_3\,.\,COOEt \xrightarrow{NaOEt} CH_3COCH_2\,.\,C\begin{cases}ONa\\CH_3\\OEt\end{cases} \longrightarrow CH_3COCH_2COCH_3$$

On the other hand, with chloroacetic ester, a glycidic ester is obtained (see also p. 417) :—



(134) (135)

When one or more of the substituent groups of the glycidic ester structure are aromatic, the glycidic ester is easily isolated ; in the case cited, although the glycidic ester (134) can be obtained pure, it readily passes into the aldehyde (135).

Other examples of the reactivity of the hydrogen atoms of acetone are :—

(*a*) The formation of a dibenzal compound,

$$C_6H_5CH = CH . CO . CH = CHC_6H_5$$

m. 112°, which is used as a means of identification.

(*b*) The formation of a sodio-derivative, best obtained by the action of sodamide on acetone. This sodio-derivative reacts readily with alkyl halides giving higher ketones :—

$$C_6H_{13}I + NaCH_2COCH_3 \longrightarrow C_6H_{13}CH_2COCH_3$$

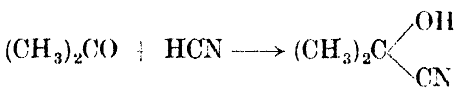
(*c*) The reaction between acetone and nitrous acid in the presence of hydrochloric acid :—

$$CH_3COCH_3 + ONOH \longrightarrow CH_3COCH = N . OH$$

The product obtained—*iso*-nitrosoacetone, is also the oxime of pyruvic aldehyde, and is converted to this substance and hydroxylamine by acid hydrolysis.

Reactions of acetone involving the carbonyl group include :—

(*a*) The addition of hydrogen cyanide to give the cyanhydrin :—



$$(CH_3)_2CO + HCN \longrightarrow (CH_3)_2C{<}^{OH}_{CN}$$

Good yields are not easily obtained by addition to the ketone direct, and the best way of obtaining the cyanhydrin in good yield is to allow the bisulphite compound of acetone to react with a solution of sodium cyanide.

(*b*) The reaction of sodium bisulphite and acetone is somewhat exceptional, as it does not take place readily with higher ketones (methyl ethyl ketone excepted). The crystalline addition compound can be recrystallised and serves to give pure acetone on decomposition by warming with sodium carbonate solution. The purification of acetone is, however, much more easily accomplished by dissolving sodium iodide in twice its weight of acetone. On standing the solution crystals of

$$NaI . 3(CH_3COCH_3)$$

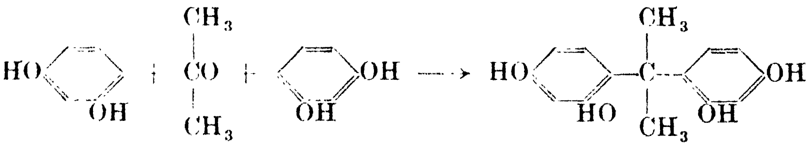
separate, and after draining and washing are decomposed by water, the pure acetone being removed from the solution by careful fractionation.

It may be added that where purity is of paramount importance, fractionation and distillation of acetone should be carried out in the dark. Ciamician and Silber have shown that in sunlight the reaction

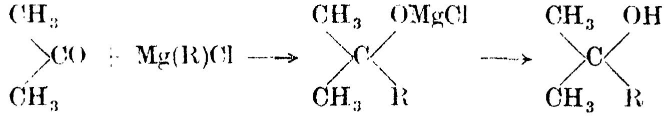
$$CH_3COCH_3 + H_2O \longrightarrow CH_3COOH + CH_4$$

proceeds to an appreciable extent.

(*c*) The oxygen of acetone reacts readily with the ring hydrogen of phenols giving rise to $\beta\beta$-diarylpropane derivatives :—

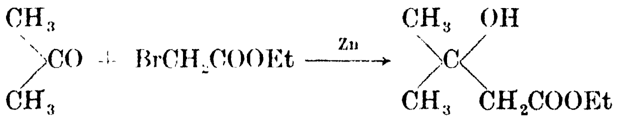


(*d*) Although acetone reacts with the Grignard reagent to give a tertiary alcohol :—

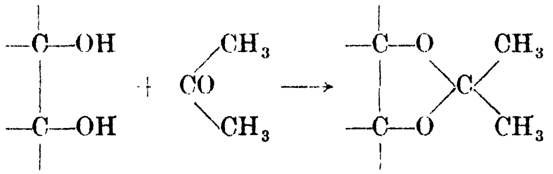


the yields are poor, and it is preferable to proceed direct from an ester. The difficulty in obtaining a satisfactory yield of tertiary alcohol is due to the Grignard reagent inducing the acetone to undergo an aldol condensation, and also to form mesityl oxide and phorone.

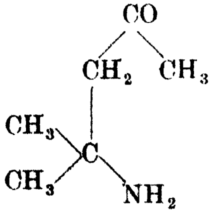
Much better results are obtained from the Reformatski reaction, in which acetone is treated with zinc and an α-bromo ester, *e.g.* :—



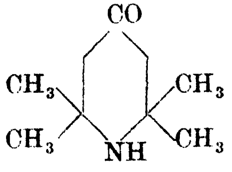
(*e*) As a further example of reactivity through the carbonyl group of acetone, the formation of cyclic acetals may be cited. Thus, when acetone reacts with ethylene glycol or glucose a stable acetal ring is obtained :—



The reaction between ammonia and acetone is complex ; the formation of mesityl oxide and phorone are induced by the ammonia independently of the formation of diacetone-amine (136) and triacetone-amine (137) :—



(136)



(137)

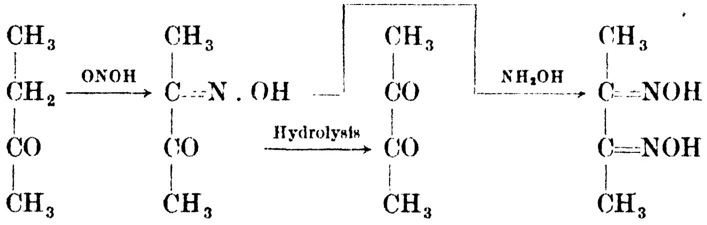
The direct action of chlorine on acetone is to give the mono- and dichloro derivatives. Monochloroacetone is a colourless liquid obtained from cold acetone by the action of chlorine in the presence of ground marble, which decomposes the hydrochloric acid formed. It is a lachrymatory substance, b. 119° ; if the chlorination is pursued both the *as*- and *s*-dichloro derivatives are obtained, and complete substitution of the hydrogen of acetone can be accomplished. Most halogen derivatives of acetone are lachrymators.

With phosphorus halides, the reaction takes an entirely different course ; it is usual to see the statement that 2, 2-dichloropropane is the product of the reaction between phosphorus pentachloride and acetone, but this is only partly true, more 2-chloropropene $CH_3CCl{=}CH_2$ being obtained, and a substantial amount of the acetone being converted to mesityl oxide and phorone, which, with phosphorus pentachloride, give their own particular halogen compounds. The most satisfactory way of converting acetone to dichloropropane is with oxalyl chloride :—

$$CH_3COCH_3 + ClCO\,.\,COCl \longrightarrow CH_3C(Cl)_2CH_3 + CO + CO_2$$

Of the higher ketones, only one or two, notably methyl ethyl ketone, (butanone-2), are available industrially. There are, however, many simple aliphatic ketones which have been prepared, and some of these are listed in Table XIII. A number of the higher ketones are found in plants, and other natural sources. Thus, methyl amyl ketone (heptanone-2) and methylheptylketone are found in Roquefort cheese, and, indeed, many cheeses owe their specific flavour, in part, at least, to the ketones of this series. Nonanone-2, decanone-2 and undecanone-2, are all found in oil of rue, in which the latter predominates.

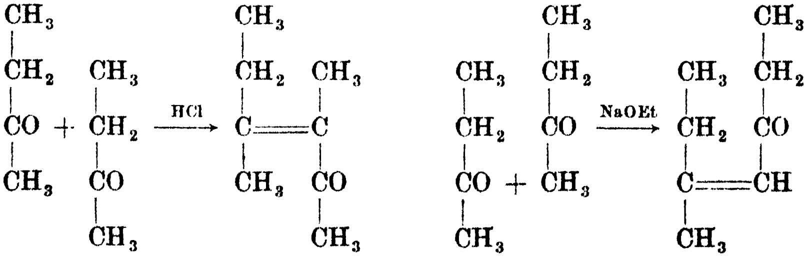
Methyl ethyl ketone is obtained industrially from butanol-2 by catalytic oxidation ; as a ketone it gives most of the characteristic reactions of the group, and is particularly noted for its formation of diacetyl monoxime by the action of nitrous acid. From this monoxime, diacetyl (138) may be obtained, or by the action of hydroxylamine it may be converted to dimethylglyoxime (139).



$$CH_3CH_2COCH_3 \xrightarrow{ONOH} CH_3C{=}N\,.\,OH\,COCH_3 \xrightarrow{Hydrolysis} CH_3COCOCH_3 \xrightarrow{NH_2OH} CH_3C({=}NOH)C({=}NOH)CH_3$$

(138) (139)

The possibilities associated with 'aldol' condensations with methyl ethyl ketone are complex, as both the $—CH_2$ and $CH_3—$ adjacent to the carbonyl group can react. In the presence of acids, the methylene group is the main reactant (140) ; with sodium ethylate, the terminal methyl group is principally involved (141).



$$CH_3CH_2COCH_3 + CH_3CH_2COCH_3 \xrightarrow{HCl} CH_3CH_2C(CH_3){=}C(CH_3)COCH_3$$

$$CH_3CH_2COCH_3 + CH_3CH_2COCH_3 \xrightarrow{NaOEt} CH_3CH_2C(CH_3){=}CHCOCH_2CH_3$$

3, 4-Dimethyl 3-hexenone-2 **3-Methyl 3-heptenone-5**

(140) **(141)**

Many chemists regard the simple aliphatic ketones as methyl derivatives of acetone ; indeed, all the series is known :—

	Relation to acetone	Name
$CH_3 . CH_2COCH_3$	Methyl-	Butanone-2 (Methyl ethyl ketone). (For properties, see above)
$(CH_3)_2CHCOCH_3$	*as*-Dimethyl-	2-Methylbutanone-3 (Methyl*iso*propyl ketone obtained by hydrolysis of trimethyl-ethylene dichloride
$CH_3 . CH_2COCH_2 . CH_3$	*s*-Dimethyl-	Pentanone-3 (Diethylketone)
$(CH_3)_2CHCOCH_2CH_3$	*as*-Trimethyl-	?-Methylpentanone-3 (Ethyl*iso*propylketone)
$(CH_3)_3C . COCH_3$	*s*-Trimethyl-	2, 2-Dimethylbutanone-3. Pinacone (best obtained from pinacol)
$(CH_3)_3C . CO . C(CH_3)_3$	Hexamethyl-	2, 2, 4, 4 Tetramethylpentanone-3. Pivalone

The main point of interest in this series is the inability of the last compound (pivalone) to give reactions with reagents such as hydroxylamine, hydrazine, etc. ; this appears to be a genuine *steric*, or volume, factor.

Pivalone may be prepared by the direct alkylation of di-*iso*propylketone with sodamide and dimethyl sulphate :—

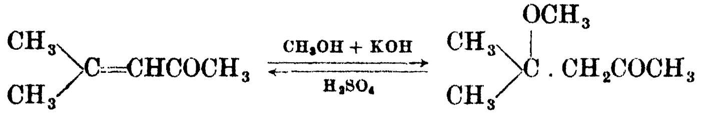
$$(CH_3)_2CHCOCH(CH_3)_2 \xrightarrow{Me_2SO_4 + NaNH_2} (CH_3)_3C . CO . C(CH_3)_3$$

UNSATURATED KETONES

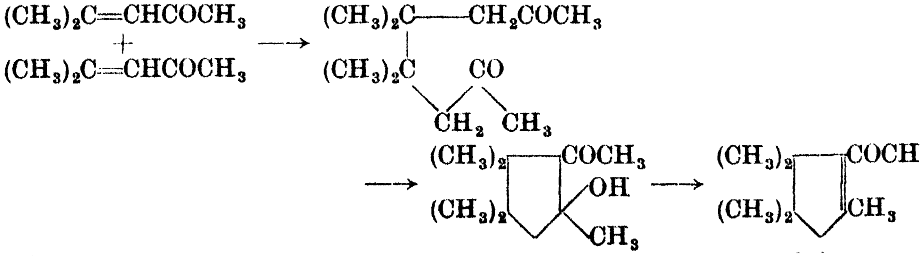
Apart from vinylmethyl ketone, mesityl oxide, and phorone, the majority of unsaturated aliphatic ketones are related to the terpene family.

Vinylmethylketone (1-butenone-3) is obtained by condensing formaldehyde and acetone to butanol-1, one-3 and dehydrating this to 1-butenone-3. It is a liquid with an extraordinarily powerful odour, and polymerises readily to a dimer, analogous to disacryl.

Mesityl oxide can be made by heating acetone under pressure with zinc chloride, and is a colourless liquid with a peppermint-like odour. It may also be obtained by the catalytic dehydration of diacetone alcohol. The methyl ether of this alcohol is regenerated when mesityl oxide is heated with methanol and alkalies ; this appears to be a direct addition of methanol at the double bond :—



In addition, mesityl oxide can easily be reduced to methyl *iso*butyl ketone, and methyl *iso*butyl carbinol, both of which are produced industrially by this route. With mild reducing agents an intermediate phase is observable, leading to the isolation of pentamethyl *cyclo*pentenyl methyl ketone (142), by way of an intramolecular aldol condensation :—



Phorone, $(CH_3)_2C{=}CH\,.\,CO\,.\,CH{=}C(CH_3)_2$, accompanies mesityl oxide in all reactions calculated to produce that compound, and may be obtained in substantial yield by adjustment of the conditions of dehydration of acetone.

Among the unsaturated ketones associated with the terpene family are :—

2-Methyl-2-heptenone-6 (Methyl heptenone), b. 171°.

2, 6-Dimethylundecatriene-2, 6, 8-one-1 (ψ-ionone), obtained by the condensation of citral and acetone.

3, 3, 6-Trimethylheptadiene-1, 5-one-4 (Artemesia ketone),

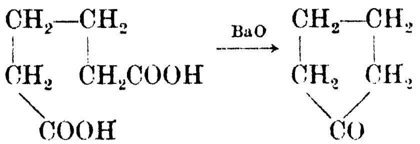
$$CH_2{=}CH\,.\,C(CH_3)_2COCH{=}C(CH_3)_2.$$

These substances are to be further discussed under the heading of 'terpenes'.

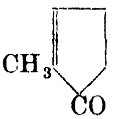
Cyclic Ketones

The higher members of the cyclic ketone series are specially considered in the Appendix to this chapter. The present remarks are confined to the five-, six- and seven-membered rings.

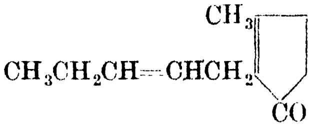
*Cyclo*pentanone is best obtained by distilling a mixture of adipic acid and anhydrous baryta, when a yield of over 70 per cent. of the ketone is obtained :—



*Cyclo*pentanone is a colourless liquid b. 130°, which has all the normal properties of an aliphatic ketone. Many derivatives of the *cyclo*pentanone ring have been prepared; methyl *cyclo*pentenone-5 (143) is found in the products of redistillation of wood tar. In jasmone, a concentrate from jasmine-oil, the active principle appears to be a methyl pentenyl-*cyclo*pentenone (144).

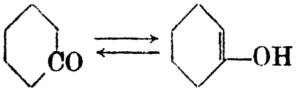


(143)



(144)

*Cyclo*hexanone is best obtained by the catalytic oxidation of *cyclo*hexanol, and is prepared by this method, industrially, in large quantities, for use as a solvent. It is an intensely stable compound with a pleasant odour, and appears to contain an appreciable percentage of its enol form (145).



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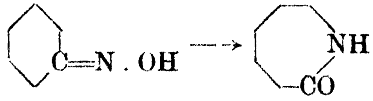
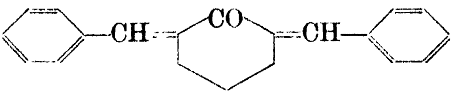


(146) (147)

Vigorous oxidation of *cyclo*hexanone gives a good yield of adipic acid. In most ways *cyclo*hexanone behaves as a normal ketone; its oxime (146), however, isomerises to the seven-membered ring lactam (147) on treatment with sulphuric acid; this is probably an internal Beckmann rearrangement.

Although the main reactions of *cyclo*hexanone are those associated with the true carbonyl group, the existence of keto-enol tautomerism is sufficient to lead to derivatives of the enol form. Thus, *cyclo*hexanone may be acetylated to acetyl *cyclo*hexenol by the use of acetic anhydride.

In addition, the presence of the carbonyl group in the ring confers on *cyclo*hexanone ability to condense through the adjacent methylene groups. It, therefore, will condense with benzaldehyde to give a dibenzal*cyclo*hexanone (148), a substance which owes its deep yellow colour to the conjugated unsaturation.



(148)

*Cyclo*heptanone (suberone), is best obtained by distilling an intimate mixture of suberic acid and anhydrous baryta ; about 60 per cent. yields are obtained of the cyclic ketone, which is a colourless oil, b. 180°, with a pleasant smell of peppermint. Suberone was the starting point for Willstätter's researches on the unsaturated seven-membered ring hydrocarbons, culminating in the synthesis of *cyclo*heptatriene (*q.v.*).

KETONES CARRYING AN AROMATIC GROUP

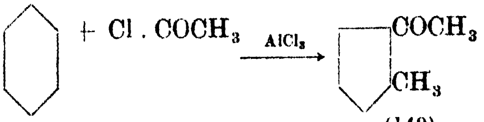
The general methods cited in previous pages are often capable of yielding a ketone in which one or both of the groups attached to the carbonyl are aromatic in character. On the other hand, the Friedel-Crafts reaction, between an aromatic structure and an acid chloride or anyhdride is a valuable additional method which is available in this field. The details of this reaction have been discussed in an Appendix to Chapter III.

The conventional use of an acid chloride with aluminium chloride is capable of a wide variety of modifications. Thus, tin or titanium chlorides may be used in place of aluminium chloride ; indeed, tin tetrachloride is to be preferred for the acylation of furane or its derivatives. The acid chloride may be replaced by anhydride or even the acid itself. Groggins and his co-workers,[1] in a detailed survey of this reaction, showed that an excellent yield of acetophenone could be obtained from benzene and acetic acid in the presence of anhydrous aluminium chloride.

Having regard to the aromatic component, nearly all substituted benzene rings, fused benzene rings, or their heterocyclic analogues will take part in the Friedel-Crafts reaction with acyl compounds. With substituted benzene derivatives the entering group usually takes an *ortho-* or *para*-position ; structures in which the existing substituents are sufficiently 'negative' to warrant the prediction of *meta*-substitution, e.g. nitro, are usually incapable of giving an acyl derivative by the Friedel-Crafts method.

When naphthalene is submitted to the Friedel-Crafts reaction in carbon disulphide solution, the product is almost exclusively the α-acyl derivative ; in nitrobenzene a preponderance of β-acyl derivative is observed, but the α-compound is also present. If an α-substituent is already present, the entering group will take up the 2-, or 4-position ; β-compounds usually yield 1-, or 6-acyl derivatives.

Anthracene gives a mixture of 1-, 2- and 9-acyl derivatives. The reaction is not entirely confined to aromatic hydrocarbons, and will proceed with *cyclo*pentane and *cyclo*hexane, although in the latter case the product is largely 1-methyl-2-acetyl*cyclo*pentane (149) an extrusion reaction having accompanied the Friedel-Crafts reaction :—



(149)

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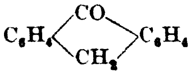
[1] Groggins, Nagel and Stirton, *Ind. Eng. Chem.*, 1934, **26**, 1313.

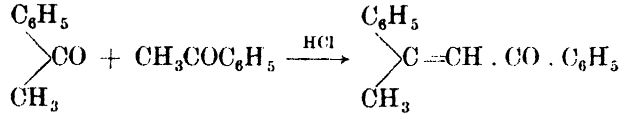
The physical properties of some of the more commonly encountered aromatic ketones are given in Table XIV. In general, their chemical behaviour shows a remarkable analogy with that of the simple aliphatic ketones; thus the α-hydrogen atoms of acetophenone enter into a reaction reminiscent of the formation

TABLE XIV

Some Aromatic Ketones

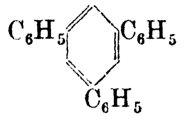
Systematic name	Formula	M.P.	B.P.	Common name
Methyl phenyl ketone	$C_6H_5COCH_3$	20°	202°	Acetophenone
Ethyl phenyl ketone	$C_6H_5COC_2H_5$	—	210°	Propiophenone
Propyl phenyl ketone	$C_6H_5COC_3H_7$	—	222°	Butyrophenone
Butyl phenyl ketone	$C_6H_5COC_4H_9$	—	237°	Valerophenone
Amyl phenyl ketone	$C_6H_5COC_5H_{11}$	—	133°/14 mm.	Capronophenone
Hexyl phenyl ketone	$C_6H_5COC_6H_{13}$	—	115°/15 mm.	—
Undecyl phenyl ketone	$C_6H_5COC_{11}H_{23}$	47°	—	Lauroylbenzene
Pentadecyl phenyl ketone	$C_6H_5COC_{15}H_{31}$	59°	—	Palmitylbenzene
iso-Butyl phenyl ketone	$C_6H_5COCH_2CH(CH_3)_2$	—	230°	*iso*-Valerophenone
ter-Butyl phenyl ketone	$C_6H_5COC(CH_3)_3$	—	220°	—
iso-Amyl phenyl ketone	$C_6H_5CO(CH_2)_2CH(CH_3)_2$	—	240°	—
3-Pentyl phenyl ketone	$C_6H_5COCH(C_2H_5)_2$	—	230°	Diethylacetophenone
Methyl-*p*-tolylketone	$CH_3C_6H_4COCH_3$	—	224°	*p*-Acetyl-toluene
Methyl-(2, 5-dimethyl phenyl) ketone	$(CH_3)_2C_6H_3COCH_3$	—	224°	Acetyl-*p*-xylene
Methyl-(2, 4, 6-trimethyl phenyl) ketone	$(CH_3)_3C_6H_2COCH_3$	—	235°	Acetylmesitylene
Diphenyl ketone	$C_6H_5COC_6H_5$	49°	306°	Benzophenone
α-Naphthyl methyl ketone	$C_{10}H_7COCH_3$	34°	295°	α-Acetonaphthone
β-Naphthyl methyl ketone	$C_{10}H_7COCH_3$	—	305°	β-Acetonaphthone
Fluorenone	$(C_6H_4)_2CO$	84°	341°	
Anthrone	 $C_6H_4{<}\begin{matrix}CO\\CH_2\end{matrix}{>}C_6H_4$	155°	—	

of mesityl oxide from acetone, yielding, in this case, the diphenyl analogue of mesityl oxide, dypnone (150)



$$\begin{matrix}C_6H_5\\ \quad\rangle CO\\ CH_3\end{matrix} + CH_3COC_6H_5 \xrightarrow{HCl} \begin{matrix}C_6H_5\\ \quad\rangle C{=}CH\,.\,CO\,.\,C_6H_5\\ CH_3\end{matrix}$$

(150)

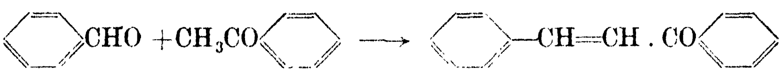


(151)

If stronger acid be used, and the reaction prolonged, triphenylbenzene (151) is obtained, a reaction which is analogous with the formation of mesitylene.

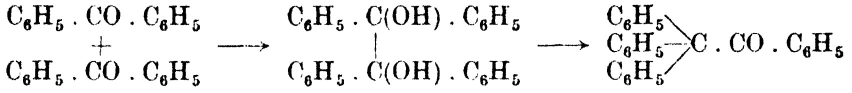
As might be expected by analogy with simpler compounds, the chlorination or bromination of acetophenone takes place in the side-chain, leading to ω-chloro- or ω-bromo acetophenone. These two substances, often termed phenacyl chloride and phenacyl bromide are strong lachrymators.

The partially aromatic ketones condense readily with aldehydes, the elements of water being lost and an unsaturated ketone being obtained. Probably the most important example of this reaction is the condensation of benzaldehyde and acetophenone to give chalcone (152) :—



(152)

The analogy in behaviour between aromatic and aliphatic ketones persists even when both groups are aromatic, as in benzophenone. This compound, for example, is easily reduced to benzpinacol (tetraphenyl ethylene glycol) (153) and, as with pinacol itself, the tetraphenyl derivative yields the corresponding pinacone (154) on dehydration :—



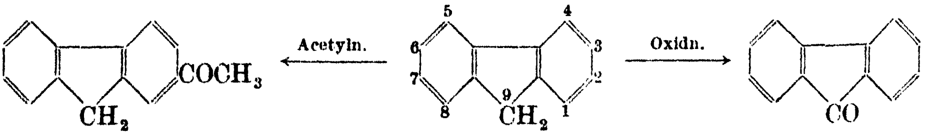
$$\begin{matrix}C_6H_5\,.\,CO\,.\,C_6H_5\\ +\\ C_6H_5\,.\,CO\,.\,C_6H_5\end{matrix} \longrightarrow \begin{matrix}C_6H_5\,.\,C(OH)\,.\,C_6H_5\\ |\\ C_6H_5\,.\,C(OH)\,.\,C_6H_5\end{matrix} \longrightarrow \begin{matrix}C_6H_5\\ C_6H_5\\ C_6H_5\end{matrix}\!\!>C\,.\,CO\,.\,C_6H_5$$

(153) (154)

Of the ketones derived from fused or condensed aromatic or semi-aromatic rings, three main classes are encountered :—

(1) The simple acyl (mainly acetyl) derivatives.
(2) The cyclic ketones where an isolated methylene group (as in fluorene → fluorenone) has been converted to a carbonyl group.
(3) The symmetrical ketones analogous to the di-aryl methanes (e.g. di-α-naphthyl ketone).

As an example of the first group we may consider the acetylation of naphthalene which, with acetyl chloride and in the presence of anhydrous aluminium chloride proceeds according to the nature of the solvent used ; carbon disulphide gives the α-derivative almost exclusively, whilst with nitrobenzene β-acetylnaphthalene preponderates.[1] With anthracene varying proportions of the 1-, 2- and 9- acetyl derivatives are formed, whilst fluorene (156) acetylates almost wholly in the 2-position (155) ; on the other hand, fluorene is readily oxidised to the cyclic ketone, fluorenone (157), a yellow crystalline compound which has many ketonic properties.



(155) (156) (157)

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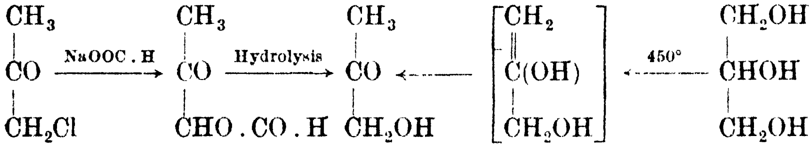
[1] Chopin, *Bull. Soc. Chim.*, 1924, **35**, 613

Phenanthrene appears to be acetylated best in nitrobenzene solution,[1] when the 3-acetyl and 2-acetyl derivatives are obtained in the proportions 4 : 1. On the other hand, 9, 10-dihydrophenanthrene acetylates to give the 2-acetyl derivative with almost theoretical yield.[2]

HYDROXYKETONES (KETOLS)

The ketols form a small but interesting group of compounds, usually subdivided into α-, β-, γ-, etc., ketols according to the relative positions of the carbonyl and hydroxyl groups. The term 'ketol' is restricted to the aliphatic series, or to those aromatic substances in which both carboxyl and hydroxyl groups are situated in the same side-chain.

The Table XV shows the names, formulæ and physical constant of a few representative ketols. The ketol most commonly encountered is propanol-1, one-2, or 'acetol' (160), usually obtained from monochloroacetone (158) by reaction with sodium formate and hydrolysis of the intermediate ester (159). Industrially, acetol can be obtained by passing the vapour of glycerol (161) over pumice heated to 450°.



$$\begin{array}{c}CH_3\\|\\CO\\|\\CH_2Cl\end{array}\xrightarrow{NaOOC.H}\begin{array}{c}CH_3\\|\\CO\\|\\CHO.CO.H\end{array}\xrightarrow{Hydrolysis}\begin{array}{c}CH_3\\|\\CO\\|\\CH_2OH\end{array}\longleftarrow\left[\begin{array}{c}CH_2\\\|\\C(OH)\\|\\CH_2OH\end{array}\right]\xleftarrow{450^\circ}\begin{array}{c}CH_2OH\\|\\CHOH\\|\\CH_2OH\end{array}$$

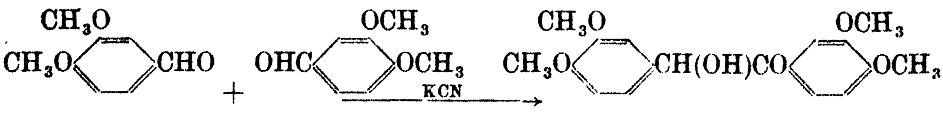
(158) (159) (160) (161)

Butanol-2, one-3 is more commonly called 'acetoin', and is the parent of the large family of 'oin' compounds, of which benzoin is probably the most widely known member. Acetoin, a substance m. 15°, b. 148° is obtainable by the partial reduction of diacetyl by zinc dust and acetic acid, but is made industrially by certain types of carbohydrate fermentation. There is some ground for believing that, during the fermentation, acetoin is produced from acetaldehyde by a reaction which may be expressed

$$2CH_3CHO \longrightarrow CH_3CH(OH)COCH_3.$$

Both diacetyl and 2, 3-butylene glycol are obtained during the fermentation.

Benzoin ($C_6H_5 . CH(OH)CO . C_6H_5$) m. 137°, is readily obtained by boiling an alcoholic solution of benzaldehyde with about one-tenth of the weight (of the aldehyde) of potassium cyanide. The reaction proceeds smoothly and on cooling the benzoin crystallises. The reaction may be considered a general one; the higher homologues of benzaldehyde, together with its alkoxy compounds form homologues or alkoxy derivatives of benzoin. The aromatic aldehydes with halogen, amino, or nitro substituents do not give benzoin compounds. Thus, veratraldehyde gives veratroin :—



Where the aromatic aldehyde is not juxtanuclear—as in phenylacetaldehyde or cinnamic aldehyde, the tendency to acyloin formation is less marked, but not entirely absent. Benzoin and its analogues are readily oxidised to the corresponding diketones, of which benzil, $C_6H_5 . CO . CO . C_6H_5$ is the prototype.

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[1] Mosettig and V. d. Kamp, *J.A.C.S.*, 1930, **52**, 3704.
[2] Burger and Mosettig, *ibid.*, 1935, **57**, 2731.

TABLE XV

SOME KETOLS

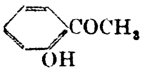
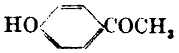
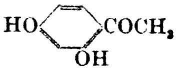
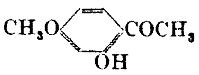
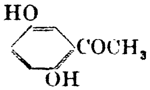
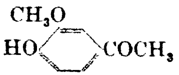
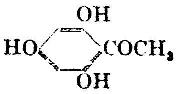
Systematic name	Formula	B.P.	Alternative names
Propanol-1, one-2	$CH_3CO\,.\,CH_2OH$	146°	Acetol, acetone alcohol. Acetyl carbinol
Butanol-1, one-2	$CH_3CH_2CO\,.\,CH_2OH$	160°	Propionyl carbinol. Ethyl ketol
Butanol-2, one-3	$CH_3CO\,.\,CH(OH)CH_3$	148°	Dimethyl ketol acetone Acetoin
Pentanol-3, one-2	$CH_3CO\,.\,CH(OH)CH_2CH_3$	77° 35 mm.	Acetyl ethyl carbinol
Pentanol-2, one-3	$CH_3CH(OH)CO\,.\,CH_2CH_3$	63°/20 mm.	Propionyl methyl carbinol
2-Methylbutanol-2, one-3	$CH_3CO\,.\,C(OH)(CH_3)_2$	142°	Trimethyl ketol
Hexanol-3, one-4	$C_2H_5CO\,.\,CH(OH)C_2H_5$	73°/20 mm.	Propioin
Octanol-4, one-5	$C_3H_7CO\,.\,CH(OH)C_3H_7$	85°/10 mm.	Butyroin
2, 5-Dimethylhexanol-3, one-4	$(CH_3)_2CH\,.\,CO\,.\,CH(OH)CH(CH_3)_2$	83°/26 mm.	*iso*-Butyroin
Decanol-5, one-6	$C_4H_9CO\,.\,CH(OH)C_4H_9$	156° 120 mm.	Valeroin
2, 2, 5, 5-Tetramethylhexanol-3, one-4	$(CH_3)_3C\,.\,CO\,.\,CH(OH)\,.\,C(CH_3)_3$	80°/10 mm.	(m. 81°) Pivaloin
Dodecanol-6, one-7	$C_5H_{11}CO\,.\,CH(OH)C_5H_{11}$	131°/8 mm.	Caproin
Butanol-1, one-3	$CH_3CO\,.\,CH_2CH_2OH$	110°/130 mm.	β-Acetoethyl alcohol
Pentanol-2, one-4	$CH_3CO\,.\,CH_2CH(OH)CH_3$	176°	Hydracetyl acetone
2-Methylpentanol-2, one-4	$CH_3CO\,.\,CH_2C(OH)(CH_3)_2$	164°	Diacetone alcohol

There is an exact parallel between the behaviour of benzaldehyde and furaldehyde in forming this type of copulated compound, and furoin and furil have a considerable similarity to benzoin and benzil.

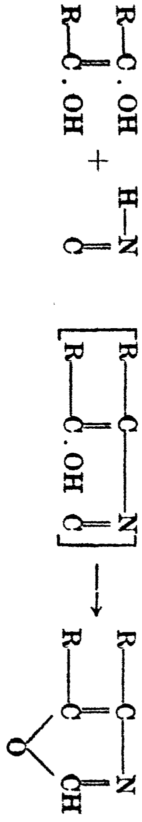
Benzoin and its homologues are able to give reactions which in many cases lead to the view that they exist in an enolic condition, $R\,.\,C(OH){=}C(OH)\,.\,R$.

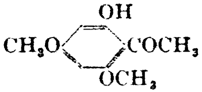
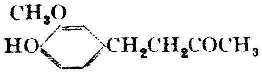
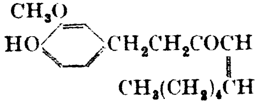
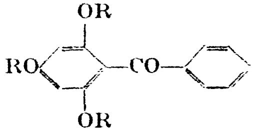
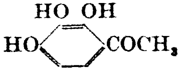
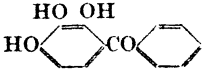
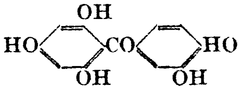
TABLE XVI

SOME HYDROXY-ARYL KETONES

Name	Formula	M.P.	Remarks
o-Hydroxyacetophenone		b. 213°	Occurs naturally in the oil from *Chione glabra* wood
m-Hydroxyacetophenæ		93°	
p-Hydroxyacetophenone		108°	The aglycone of picein, a glycoside from willow and fir
2, 4-Dihydroxyacetophenone (Resacetophenone)		142°	From resorcinol, acetic acid and zinc chloride
4-Methoxy-2-hydroxy acetophenone (Pæonol)		50°	The aglycone from a glycoside of Pæony root
2, 5-Dihydroxyacetophenone (Quinacetophenone)		202°	From hydroquinone, acetic acid and zinc chloride
m-Methoxy-*p*-hydroxy acetophenone		115°	From *Apocynum cannabinum*
Phloracetophenone		—	From phloroglucinol, acetic acid and zinc chloride

Thus, with hydrogen cyanide in the presence of sulphuric acid they yield 4, 5-substituted oxazoles :—

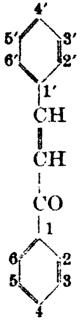
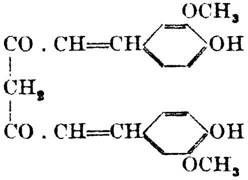


Phloracetophenone dimethyl ether		—	Found in the volatile oil of *Blumea balsifera*
Zingerone		41°	(See Appendix II.) A sharp-tasting constituent of ginger
Shogaol		—	(See Appendix III)
PHLOROBENZOPHENONE			
—4-Methyl ether (Cotoin)		166°	The bark of the coto-shrub (a kind of laurel) contains these and other substances, which have been used medicinally. They have all been synthesised. (Späth and Fuchs, *Monats*, 1921, **42**, 267)
—2, 4-Dimethyl ether (Hydrocotoin)		131°	
—2, 4, 6-Trimethylether (Methylhydrocotoin)		98°	
		115°	
—3, 4-Methylenedioxyhydrocotoin (Protocotoin)		141°	
THE PIGMENT HYDROXYKETONES			
Gallacetophenone		168°	From pyrogallol, acetic acid and zinc chloride
Gallobenzophenone		—	From pyrogallol, benzoic acid and zinc chloride. Known as Alizarin Yellow A, it is used as a mordant dye
Maclurin (Pentahydroxybenzophenone)		200°	A colouring matter from fustic (*Morus tinctoria*)

Many hydroxyketones are known in which the aromatic nucleus carries the hydroxyl group, the keto-group being situated in a side-chain. These are illustrated by the examples in Table XVI.

TABLE XVI—(*Continued*)

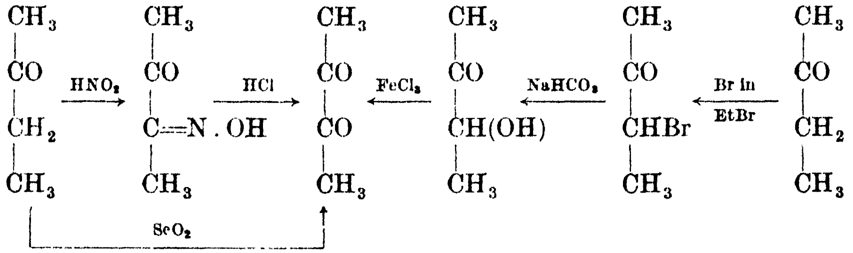
SOME HYDROXY-ARYL KETONES

Name	Formula	M.P.	Remarks
CHALKONES			
Salipurol (2, 4, 4′, 6-tetrahydroxychalkone		—	Occurs as a glycoside in certain willow species
Carthamin (2, 3, 4, 4′, 6-pentahydroxy chalkone)		—	Contained, as the active pigment, in Safflower the dried petals of *Carthamus tinctorius*)
Butein (2, 4, 3′, 4′-tetrahydroxychalkone)		215°	From the petals of *Butea frondosa*
Curcumin		178°	The active yellow pigment from turmeric the dried and ground root of *Curcuma tinctoria*

DIKETONES

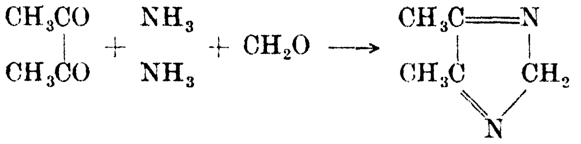
It is customary to divide the diketones into families depending on the relative positions of the carbonyl groups; in α-diketones the two carbonyls are adjacent; in β-diketones they are separated by a single carbon; the γ-diketones have the separation effected by two carbon atoms, and it is customary to refer to higher diketones by the numerical descriptions, 1, 5-, 1, 6-, 1, 10-, etc.

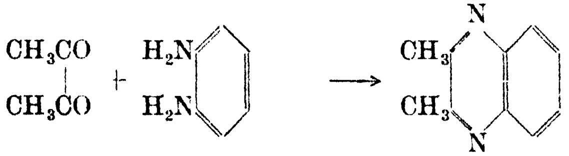
α-Diketones.—The prototype, diacetyl, $CH_3CO \cdot COCH_3$ is a pale yellow liquid b. 88°. It is obtained industrially by the fermentation of glucose, through the intermediary of acetoin. For small quantities, the preparation from methyl ethyl ketone outlined in the formulæ below may be used :—



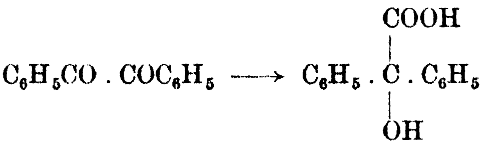
Two other modes of proceeding from methyl ethyl ketone to diacetyl are shown in the diagram above, direct oxidation with selenium dioxide and conversion through 3-bromobutanone-2 which is obtainable from butanone-2 and bromine in ethyl bromide. Acetoin is obtained by hydrolysing the bromo-compound in bicarbonate solution and may be converted to diacetyl by ferric chloride oxidation.

Diacetyl is employed in dilute solution for simulating a flavour of butter, in which substance it occurs naturally. Acetyl propionyl (pentane-2, 3-dione) is also used in this way. Diacetyl is a highly reactive compound, giving glyoxalines and quinoxalines with *o*-diamines, and with formaldehyde and ammonia :—


Dimethylglyoxaline


2, 3-Dimethylquinoxaline

Benzil, $C_6H_5CO \cdot COC_6H_5$, m. 95°, is formed as yellow needles by the oxidation of benzoin, usually with nitric acid, although alkaline cupric solutions can be used equally well. It is mainly of interest for two reactions (*a*) its reduction to desoxybenzoin $C_6H_5CH_2COC_6H_5$, and (*b*) its conversion to benzilic acid (*q.v.*) by alkali fusion :—


$$C_6H_5CO \cdot COC_6H_5 \longrightarrow C_6H_5 \cdot C(COOH)(OH) \cdot C_6H_5$$

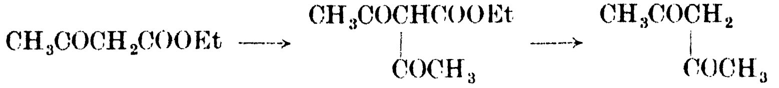
β-Diketones.—The prototype of *β*-diketones is acetylacetone,

$$CH_3CO \cdot CH_2COCH_3,$$

a liquid, b. 140°, obtained by the condensation of ethyl acetate and acetone in

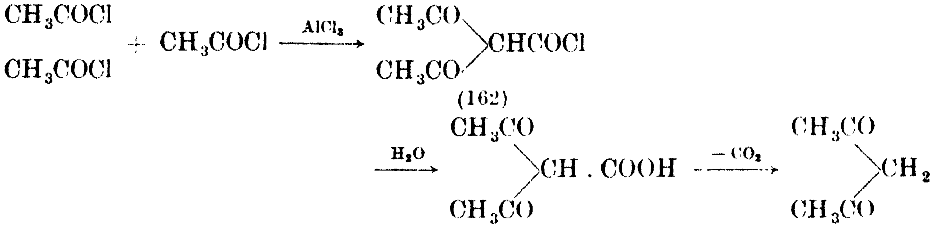
$$CH_3COOEt + CH_3COCH_3 \longrightarrow CH_3CO \cdot CH_2COCH_3$$

the presence of sodium, sodamide, or sodium hydride. It is usual to isolate the diketone by forming the copper salt, suspending the moist salt in ether and decomposing it with dilute sulphuric acid. Acetyl acetone may also be obtained from ethyl acetoacetate, by conversion to its C-acetyl derivative which gives the diketone on boiling with water :—



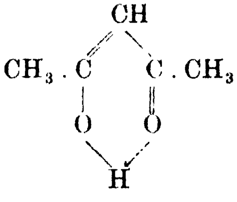
$$CH_3COCH_2COOEt \longrightarrow \begin{matrix} CH_3COCHCOOEt \\ | \\ COCH_3 \end{matrix} \longrightarrow \begin{matrix} CH_3COCH_2 \\ | \\ COCH_3 \end{matrix}$$

Acetylacetone also makes its appearance in many reactions of the Friedel-Crafts type in which either acetyl chloride or acetic anhydride come into contact with anhydrous aluminium chloride or boron trifluoride. The essential intermediate in the case of acetyl chloride appears to be diacetoacetyl chloride (162), which hydrolyses to the acid, and generates the diketone by loss of carbon dioxide :—

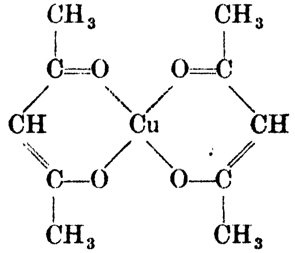


(162)

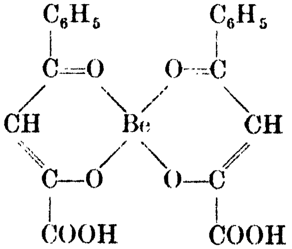
When cautiously distilled from all-glass apparatus acetylacetone appears to consist wholly of the mono-enol form, the exceptional volatility of which is accounted for by its chelate form (163). Even after standing, the equilibrium between diketo- and mono-enol form is well over on the latter side, and the formation of metallic derivatives such as the copper and beryllium salts (164) still indicates the ease with which the enol is formed. The beryllium salt is volatile, may be distilled without decomposition at 270°, and has been used to establish the valency of beryllium. The analogous beryllium derivative of benzoylpyruvic acid (165) has been resolved by Mills and his co-workers into its optical isomers, thus giving added proof of the structure of this type of compound.



(163)

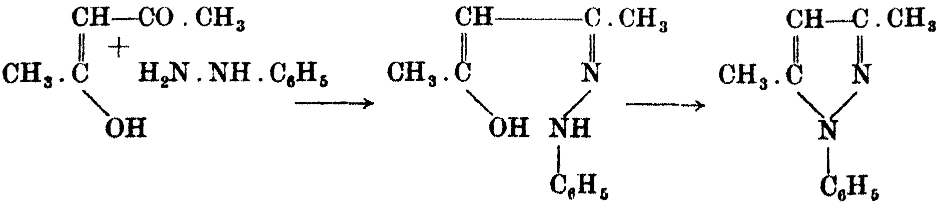


(164)



(165)

Chemically, acetylacetone is characterised by the intense activity of its central methylene group and by the fact that it forms cyclic compounds with great ease. Thus, pyrazoles are formed with aryl hydrazines



The activity of the central methylene group is described elsewhere (Chap. VIII). Homologues of acetylacetone are well known,[1] some of which are shown in Table XVII.

TABLE XVII

Some β-Diketones

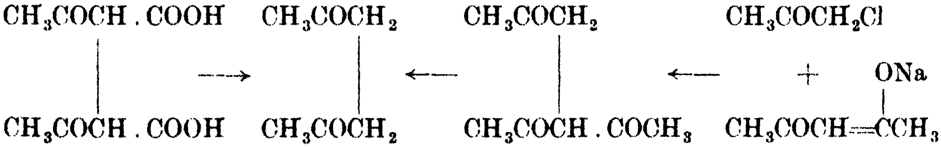
Systematic name	Formula	B.P.	Alternative name
Pentane-dione-2, 4	$CH_3COCH_2COCH_3$	140°	Acetylacetone
Hexane-dione-2, 4	$CH_3CH_2COCH_2COCH_3$	162°	Propionylacetone
Heptane-dione-2, 4	$CH_3(CH_2)_2COCH_2COCH_3$	101–102°/9 mm.	*n*-Butyrylacetone
Octane-dione-2, 4	$CH_3(CH_2)_3COCH_2COCH_3$	194°	*n*-Valerylacetone
Nonane-dione-2, 4	$CH_3(CH_2)_4COCH_2COCH_3$	211–213°/750 mm.	*n*-Hexoylacetone
Terdecane-dione-2, 4	$CH_3(CH_2)_8COCH_2COCH_3$	276°	*n*-Decoylacetone
Pentadecane-dione-2, 4	$CH_3(CH_2)_{10}COCH_2COCH_3$	m. 31–32	*n*-Dodecoylacetone
Heptane-dione-3, 5	$CH_3CH_2COCH_2COCH_2.CH_3$	176°/751 mm.	Dipropionylmethane
Octane-dione-3, 5	$CH_3(CH_2)_2COCH_2COCH_2.CH_3$	189°/758 mm.	Propionyl-*n*-butyryl methane
Nonane-dione-4, 6	$C_3H_7COCH_2COC_3H_7$	204–205°	Di-*n*-butyrylmethane

Mixed aryl-alkyl diketones are also quite common, and the prototype of this series, benzoyl acetone, $C_6H_5COCH_2COCH_3$, is readily prepared as a crystalline solid, m. 60–61°, by the Claisen condensation between acetophenone and ethyl acetate

$$C_6H_5COCH_3 + EtOOC\,.\,CH_3 \longrightarrow C_6H_5COCH_2COCH_3.$$

The condensing agent may be sodium, sodium ethoxide or sodamide.

Acetonylacetone ($CH_3COCH_2CH_2COCH_3$) is representative of the γ- or 1, 4-diketones. It is prepared by heating diacetyl-succinic acid (166), when decarboxylation ensues :—



(166) (167) (168) (169)

It may also be obtained by the action of monochloroacetone on sodium acetylacetone (169). An intermediate triketone (168) is obtained which is easily hydrolysed to acetonylacetone (167). The most characteristic property of the 1, 4-diketones is the ease with which they form five-membered cyclic ring compounds, apparently through the dienolic form (170).

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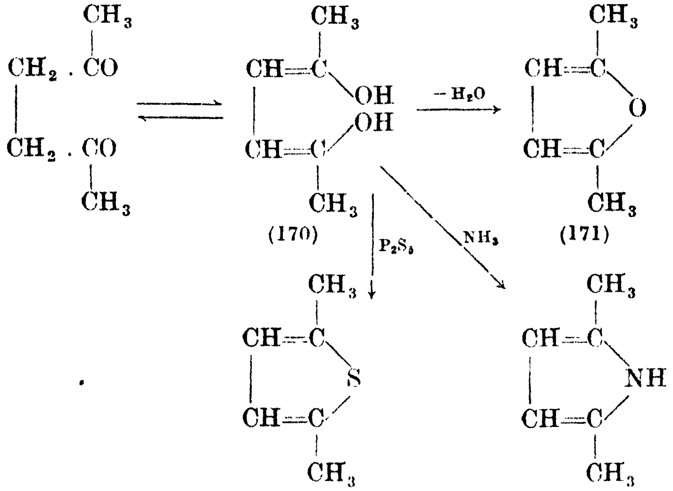
[1] Morgan (and co-workers), *J.C.S.*, 1924, **125**, 740, 756, 760, 1271 ; *ibid.*, 1925, **127**, 2619, 2620.

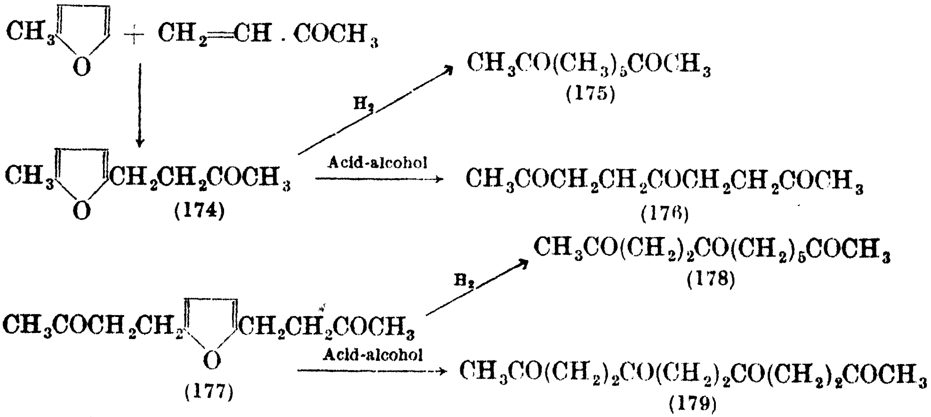
Dehydration leads to furan compounds (171); reaction with phosphorus pentasulphide gives thiophen analogs (172) and derivatives of pyrrole (173)



(170) (171) (172) (173)

are obtained when the diketone is heated with ammonia. Despite this tendency to react through the dienolic form, the diketo-structure is present in normal specimens of the material, and gives its dioxime normally with hydroxylamine.

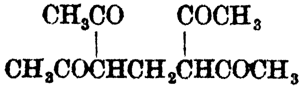
Long-chain diketones are frequently made by reversing the cyclisation that leads to the furan derivatives.[1] Thus, when methylfuran reacts with vinyl methyl ketone, a 2(5-methylfuryl) butanone (174) is obtained. This, on reduction, yields nonanedione-2, 8 (175). In the same way, the compound



(174) (175) (176) (177) (178) (179)

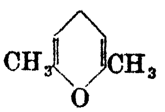
(177) obtained by the condensation of furan with two molecules of vinylmethylketone, is reduced to dodecantrione-2, 5, 10 (178). If the reduction is carried out with acid-alcohol, the corresponding tri- (176) and tetra-ketone (179) are formed.

1 : 5-Diketones are exceptionally difficult to obtain, and unless stabilised by other groups (as in (180)), cyclise to derivatives of pyran (181)



$$CH_3COCH(COCH_3)CH_2CH(COCH_3)COCH_3$$

(180)



(181)

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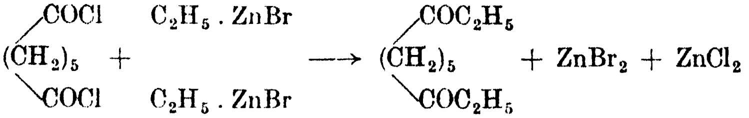
[1] Alder and Schmidt, *Ber.*, 1948, **76**, 183.

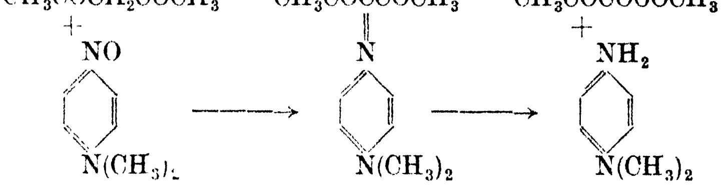
Diketones in which the two carbonyl groups are separated by more than three methylene groups are quite easy to prepare, but the carbonyl groups act independently. The simplest method of preparing them is to allow the corresponding di-acid chloride to react with an excess of zinc alkyl halide



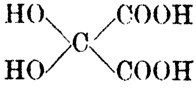
$$(CH_2)_5(COCl)_2 + 2\,C_2H_5 . ZnBr \longrightarrow (CH_2)_5(COC_2H_5)_2 + ZnBr_2 + ZnCl_2$$

TRI- AND POLY-KETONES

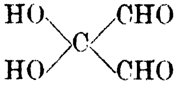
Pentane, 2, 3, 4-*trione*, $CH_3COCOCOCH_3$ is the simplest triketone, and may be obtained by condensing acetylacetone with *p*-nitrosodimethylaniline (182) giving the imine (183). On hydrolysis with acid the latter compound gives *p*-aminodimethylaniline and pentane, 2, 3, 4-trione (184). The triketone is an orange-red liquid, b. 55°/12 mm. but it easily forms a colourless hydrate. This is a characteristic of structures containing three adjacent carbonyl groups. Thus mesoxalic acid, mesoxaldehyde, triketohydroindene all share the ability to form a stable hydrate, whilst in the case of dihydroxytartaric acid (185), the property extends to the two central carbonyl groups.



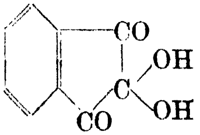
(182) (183) (184)



Mesoxalic acid hydrate

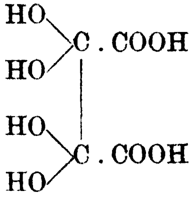


Mesoxaldehyde hydrate



Triketohydrindene hydrate

(186)



Diketosuccinic acid dihydrate
(Dihydroxytartaric acid)

(185)

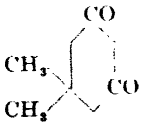
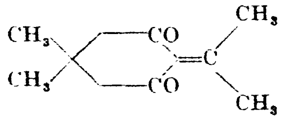
Triketohydrindene hydrate (186) is a valuable reagent for the detection and estimation of α-amino-acids with which it gives an intense blue colour.

There are, of course, many tri- and polyketones in which the carbonyl groups are separated by $—CH_2$ groups; it is not proposed to discuss these in detail, but attention is drawn to the ability of structures such as phloroglucinol, to behave as triketones (in the case cited, as 1, 3, 5-triketo*cyclo*hexane).

REACTIONS OF ALDEHYDES AND KETONES AFFECTING THE CARBONYL GROUP

Most aldehydes and ketones exhibit a series of reactions in which the oxygen of the carbonyl group is induced to combine with two atoms of hydrogen from an amino- or active methylene group, thereby engendering a series of compounds which are invaluable for isolating and characterising aldehydes and ketones.

TABLE XVIII

Substance	Formula	Generic name of product	Typical example of product
Hydroxylamine	$H_2N . OH$	Oxime	$(CH_3)_2C{=}N . OH$
Hydrazine	$H_2N . NH_2$	(1) Hydrazone (2) Azine	$C_6H_5 . CH{=}N . NH_2$ $C_6H_5 . CH{=}N . N{=}CH . C_6H_5$
Phenylhydrazine	$C_6H_5 . NHNH_2$	Phenylhydrazone	$CH_3CH{=}N . NHC_6H_5$
***p*-Bromophenylhydrazine**	$BrC_6H_4 . NHNH_2$	*p*-Bromophenylhydrazone	$CH_3CH{=}N . NHC_6H_4Br$
***p*-Nitrophenylhydrazine**	$NO_2C_6H_4NHNH_2$	*p*-Nitrophenylhydrazone	$CH_3CH{=}N . NHC_6H_4(NO_2)$
2, 4-Dinitrophenylhydrazine	$(NO_2)_2C_6H_3NHNH_2$	2, 4-Dinitrophenylhydrazone	$CH_3CH{=}N . NHC_6H_3(NO_2)_2$
2, 4, 6-Trinitrophenylhydrazine	$(NO_2)_3C_6H_2NHNH_2$	2, 4, 6-Trinitrophenylhydrazone	$CH_3CH{=}N . NHC_6H_2(NO_2)_3$
α-Naphthylhydrazine	$C_{10}H_7NHNH_2$	α-Naphthylhydrazone	$C_{10}H_7NH . N{=}CHCH_3$
Semicarbazide	$H_2NCONHNH_2$	Semicarbazone	$CH_3CH{=}N . NHCONH_2$
Phenylsemicarbazide	$C_6H_5NHCONHNH_2$	Phenylsemicarbazone	$C_6H_5NHCONH . N{=}CHCH_3$
Thiosemicarbazide	$H_2NCSNHNH_2$	Thiosemicarbazone	$CH_3CH{=}N . NH . CS . NH_2$
Carbazide	$H_2NNH . CO . NHNH_2$	Carbazone	—
Thiocarbazide	$H_2NNH . CS . NHNH_2$	Thiocarbarbazone	—
Semioxamazide	$H_2NCO . CO . NHNH_2$	Semioxamazone	—
Thiosemioxamazide	$H_2NCS . CS . NHNH_2$	Thiosemioxamazone	—
Aniline	$C_6H_5NH_2$	Anil	$C_6H_5N{=}CHC_6H_5$
5, 5-Dimethyl *cyclo*hexandione-1, 3 (Dimedon)			

The simplest substance to show this property is hydroxylamine, giving oximes with both aldehydes and ketones :—

$$R_1CO\ .\ R_2 \longrightarrow R_1\ .\ C{=}N(OH)\ .\ R_2.$$

Even formaldehyde gives an oxime, obtainable by adding formaldehyde solution to a freshly prepared solution of hydroxylamine hydrochloride which has been exactly neutralised with sodium hydroxide. Formaldoxime [1] may be extracted with ether and remains, after distillation, as a powerfully odorous volatile liquid, b. 84° ; it polymerises rapidly on standing.

Acetaldoxime is much more stable than formaldoxime, and may be prepared in a similar way.

Ketoximes are not so readily formed as aldoximes, and prolonged heating is sometimes necessary in order to induce the formation of oximes.

Apart from their value in the characterisation of aldehydes and ketones, oximes are important starting points in synthetic organic chemistry (see Vol. II).

Table XVIII shows the common substances used for condensation reactions analogous to that exhibited by hydroxylamine.

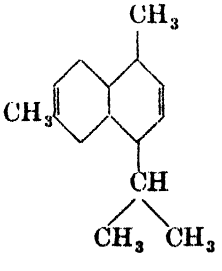
The choice of reagent for isolation or identification of an aldehyde or ketone depends, of course, on the solubilities of the products obtained. For the actual isolation where the original compound is to be regenerated, semicarbazide is the preferred reagent as simple boiling with dilute sulphuric acid will release the aldehyde or ketone. Where minute quantities of material are to be separated and characterised the nitrophenylhydrazines are usually preferred, since they give highly insoluble, but crystalline, condensation products.

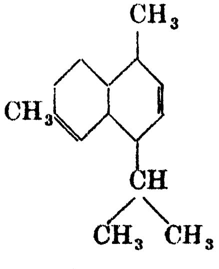
APPENDIX I

RING KETONES AND THEIR RELATION TO MUSK ODOUR

From the earliest times it has been customary to use substances with a pronounced musk odour in perfumery, and even at the present time few perfumes are considered complete without natural or synthetic musk. Vegetable sources of musk odorous substances have also been known for a long time ; apparently the common musk plant (*Mimosa moschata*), introduced into this country about a century ago from Columbia and California, has by repeated cultivation, lost its musk scent, and is now odourless. Although a few plants such as musk mallow (*Malva moschatus*), musk melon (*Curcumis melo*), musk thistle (*Carduus nutans*) and musk orchis (*Herminium monorchis*) possess the odour associated with their names, only two—sumbul (*Ferula sumbul*) and ambrette (*Abelmoschus moschatus*) are specifically cultivated for this quality.

Sumbul—a plant indigenous to the Maghian mountains of Bokhara, yields from its roots an oil with a strong musk odour, due to a ring-lactone and an unsaturated hydrocarbon, sumbulene, which is reputed to have one of the formulæ below :—





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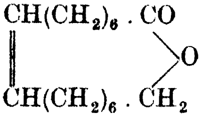
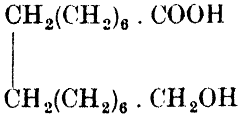
[1] Dunstan and Bossi, *J.C.S.*, 1898, **73**, 353.

Ambrette is largely grown in the Seychelles, and from its seed is obtained a strongly musk-smelling oil, the odoriferous constituent of which is ambrettolide, an unsaturated lactone of the structure (187). Such compounds have a structural relation to the animal musks, and also to the acids, such as juniperic acid (188). In Kerschbaum's researches [1] on ambrettolide he was able to confirm the proposed structure for this compound by converting it to juniperic acid, first opening the lactone ring to give the unsaturated acid (189), which on catalytic reduction gave juniperic acid.

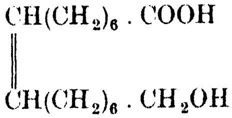


(187)



$$\begin{array}{l} CH_2(CH_2)_6 \,.\, COOH \\ | \\ CH_2(CH_2)_6 \,.\, CH_2OH \end{array}$$

(188)



$$\begin{array}{l} CH(CH_2)_6 \,.\, COOH \\ \| \\ CH(CH_2)_6 \,.\, CH_2OH \end{array}$$

(189)

Animal musks are obtained mainly from three sources :—

(1) *Hyraceum*, the dried urine of the rock-badger (*Hyrax capensis*).
(2) *Civet*, the secretion from the preputial follicles of the Abyssinian civet cat (*Viverra civetta*).
(3) *Musk*, the contents of the preputial follicle of the musk deer (*Moschus moschiferus*).

Two factors led to a somewhat slow development of our knowledge of real animal musk ; first, the very high cost of material, of which only a limited amount was available for experimental work, together with the very small percentage of the true odoriferous principle ; and, secondly, the state of knowledge concerning the cyclic substances containing more than six carbon atoms.

During the latter half of the nineteenth century, knowledge of organic chemistry grew apace, but mainly along lines concerned with the aromatic hydrocarbons. Of the few experiments which were made on rings larger than that of benzene, only a comparatively small percentage were in any way successful, and the idea gradually grew up that for some unaccountable reason rings containing more than six atoms of carbon were unstable and became progressively more unstable as their size increased. This belief was fostered by the work of Baeyer on the so-called " Strain Theory ", in which he attempted to show that rings containing five or six carbon atoms are virtually strainless, whilst those containing fewer, or more, are strained in proportion to the extent by which their rings diverge from the *cyclo*pentane structure. This theory was built up on two misconceptions, namely, the planar conception of ring structure, and a rigidly directed valency force, and has proved misleading. One consequence of the general acceptance of the theory was discouragement of research on large rings. On the other hand, Baeyer's theory was by no means without its opponents ; as early as 1890 Sachse [2] suggested the existence of non-planar forms of *cyclo*hexane—similar to the ' chair ' and ' bed ' types now generally held to accord with the properties of this group of compounds ; and in 1918 Mohr [3] extended the theory to cover strainless rings of the decahydronaphthalene class. The separation by Windaus, Hückel [4] and others of indubitable isomers of this class, including *cis*- and *trans*-decahydronaphthalene, afforded incontrovertible evidence that the Sachse-Mohr conception of strainless aplanar rings is essentially correct. The implication, as far as large rings is concerned, is that, once formed, their stability is largely independent of the number of carbon atoms ; as will be seen later, the practical difficulty is to induce the two ends of a chain, normally some considerable distance apart, to link up in ring form.

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[1] Kerschbaum, *Ber.*, 1927, **60B**, 902.

[2] Sachse, *ibid.*, 1890, **23**, 1363.

[3] Mohr, *J. Pr. Chem.*, 1918, [ii], **98**, 315.

[4] Windaus, Hückel *et al.*, *Ber.*, 1923, **56**, 95 ; Hückel, *Nach. K. Ges. Wiss. Gottingen*, 1923, 43.

Prior to the work of Mohr, Walbaum,[1] in 1906, had isolated a ketone from natural musk which appeared to be the odorous principle. The crude animal material was extracted with dry ether, the ethereal extract evaporated and subjected to distillation in a current of steam, when about 1 per cent. of an oil, b. 145–147°/4 mm. was obtained. It had an intense musk odour and, by giving a crystalline semicarbazone, revealed itself as a ketone. The empirical formula, $C_{16}H_{30}O$, and the absence of unsaturation indicates the probable presence of a single ring.

Nearly ten years later Sack [2] obtained a similar ketone (m. 31°) from civet. The empirical formula, $C_{17}H_{30}O$, and the ease with which its single double bond could be saturated, forming a dihydrocivetone, led to the supposition that it might be the cyclic ketone, *cyclo*heptadecenone. It was these investigations which led Ruzicka and his co-workers to study the large rings and to endeavour to synthesise compounds analogous to muscone and civetone.[3]

Commencing with *cyclo*nonanone, which he obtained by the thermal decomposition of thorium sebacate in vacuum, Ruzicka extended the reaction to rings with as many as thirty carbon atoms, some properties of which are shown in Table XIX. The yields of cyclic ketones gradually decrease with increase in the size of ring, exhibiting a minimum (0·15 per cent.) with *cyclo*decanone, and rising slowly thereafter.

TABLE XIX

CYCLIC RING KETONES

Number of atoms in ring	Name	M.P.	B.P.	Semi-carbazone m.p.	Remarks on odour
5	*Cyclo*pentanone	—	130°	—	—
6	*Cyclo*hexanone	—	155°	—	Almond
7	*Cyclo*heptanone	—	180°	164°	Peppermint (faint)
8	*Cyclo*öctanone	25–26°	196°	85°	Unidentifiable
9	*Cyclo*nonanone	—	96°/17 mm.	105°	Camphoraceous
10	*Cyclo*decanone	—	100°/12 mm.	200°	Camphoraceous
11	*Cyclo*undecanone	—	110°/12 mm.	200°	Camphoraceous
12	*Cyclo*dodecanone	59°	125°/12 mm.	226°	Camphoraceous
13	*Cyclo*tridecanone	32°	138°/12 mm.	207°	Cedar, faint musk
14	*Cyclo*tetradecanone	52°	155°/12 mm.	197°	Intense musk
15	*Cyclo*pentadecanone (Exaltone)	63°	120°/0·3 mm.	187°	Pure agreeable musk
16	*Cyclo*hexadecanone	56°	138°/0·3 mm.	180°	Between musk and civet
17	*Cyclo*heptadecanone (Synthetic civet)	63°	145°/0·3 mm.	191°	Intense civet
18	*Cyclo*öctadecanone	71°	158°/0·3 mm.	184°	Feeble civet
19	*Cyclo*nonadecanone	—	—	—	Almost no odour
30	*Cyclo*triacontanone	54°	—	—	No odour

The identity of synthetic *cyclo*heptadecanone (192) with that obtained by the reduction of civetone (191) reveals the basic structure of the latter ketone to be the 17-carbon ring. The assignment of the double bond to the 9-position rests on the observation that, on oxidation, the presence of dicarboxylic acids up to azelaic (193) can be detected. The absence of higher acids is only compatible with the symmetrical form. Speculation as to the biogenetic formation of civetone leads to the plausible suggestion that it arises by biological dehydration of oleic acid (190), but there is no direct evidence to support this.

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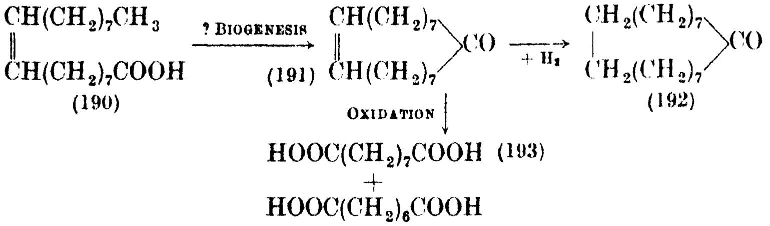
[1] Walbaum, *J. Pr. Chem.*, 1906, **73**, 488.

[2] Sack, *Ch. Ztg.*, 1915, **39**, 538.

[3] Ruzicka *et al.*, *Helv. Chim. Acta*, 1926, **9**, 249, 339, 389, 499.

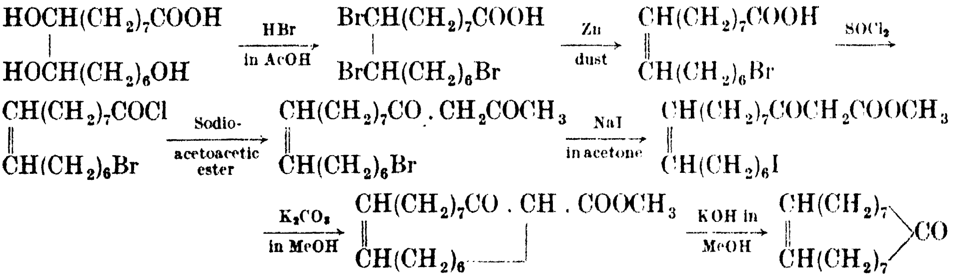


(190) (191) (192) (193)

$$\begin{matrix}CH(CH_2)_7CH_3\\ \|\\ CH(CH_2)_7COOH\end{matrix} \xrightarrow{?\ \text{Biogenesis}} \begin{matrix}CH(CH_2)_7\\ \|\\ CH(CH_2)_7\end{matrix}\!\!>CO \xrightarrow{+H_2} \begin{matrix}CH_2(CH_2)_7\\ |\\ CH_2(CH_2)_7\end{matrix}\!\!>CO$$

$$\xrightarrow{\text{Oxidation}} HOOC(CH_2)_7COOH + HOOC(CH_2)_6COOH$$

The synthesis of civetone was, for a long time, hampered by the lack of a suitable starting material. This was discovered by Hunsdiecker[1] in aleuritic acid, a 9, 10, 16-trihydroxypalmitic acid obtained by treatment of finely powdered shellac with caustic potash at ordinary temperatures. The conversion of aleuritic acid to civetone is accomplished by the stages shown below :—

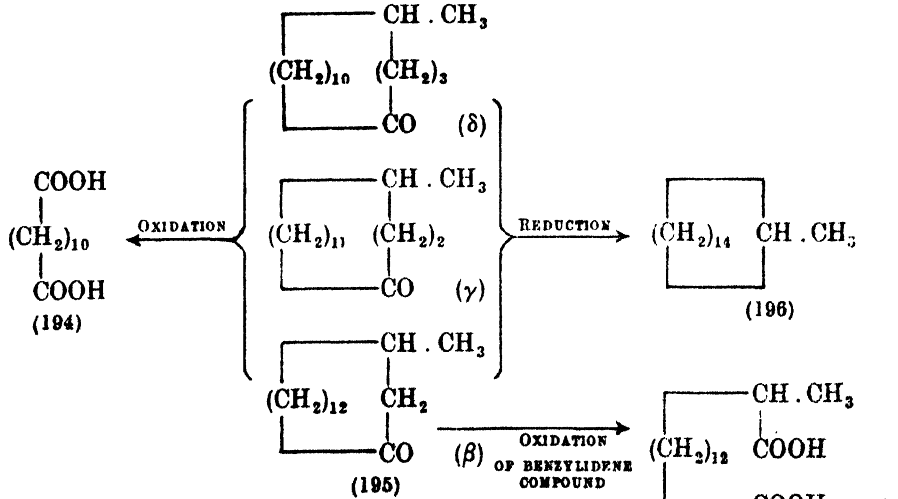


$$\begin{matrix}HOCH(CH_2)_7COOH\\ |\\ HOCH(CH_2)_6OH\end{matrix} \xrightarrow[\text{in AcOH}]{HBr} \begin{matrix}BrCH(CH_2)_7COOH\\ |\\ BrCH(CH_2)_6Br\end{matrix} \xrightarrow[\text{dust}]{Zn} \begin{matrix}CH(CH_2)_7COOH\\ \|\\ CH(CH_2)_6Br\end{matrix} \xrightarrow{SOCl_2}$$

$$\begin{matrix}CH(CH_2)_7COCl\\ \|\\ CH(CH_2)_6Br\end{matrix} \xrightarrow[\text{acetoacetic ester}]{\text{Sodio-}} \begin{matrix}CH(CH_2)_7CO\,.\,CH_2COCH_3\\ \|\\ CH(CH_2)_6Br\end{matrix} \xrightarrow[\text{in acetone}]{NaI} \begin{matrix}CH(CH_2)_7COCH_2COOCH_3\\ \|\\ CH(CH_2)_6I\end{matrix}$$

$$\xrightarrow[\text{in MeOH}]{K_2CO_3} \begin{matrix}CH(CH_2)_7CO\,.\,CH\,.\,COOCH_3\\ \|\qquad\qquad\qquad |\\ CH(CH_2)_6\text{———}\end{matrix} \xrightarrow[\text{MeOH}]{\text{KOH in}} \begin{matrix}CH(CH_2)_7\\ \|\\ CH(CH_2)_7\end{matrix}\!\!>CO$$

The pure and agreeable musk odour of synthetic *cyclo*pentadecanone, not only affords a substitute (' Exaltone ') for the natural material, but also points to some possible structural relation between the two substances. Oxidation of



(δ) (γ) (β) (194) (195) (196) (197)

muscone gave a fair yield of dodecane diacid-1, 12 (194), and on reduction, methyl-*cyclo*pentadecane (196) was obtained. As both these substances have been independently synthesised, this evidence points to one of the three structures (195) for muscone. The presence of 2-methyltetradecane diacid-1, 14 (197), among the products of oxidation of benzylidene-muscone, leaves little doubt that the β-formula (110) (3-methyl*cyclo*pentadecanone) correctly represents the structure of muscone.

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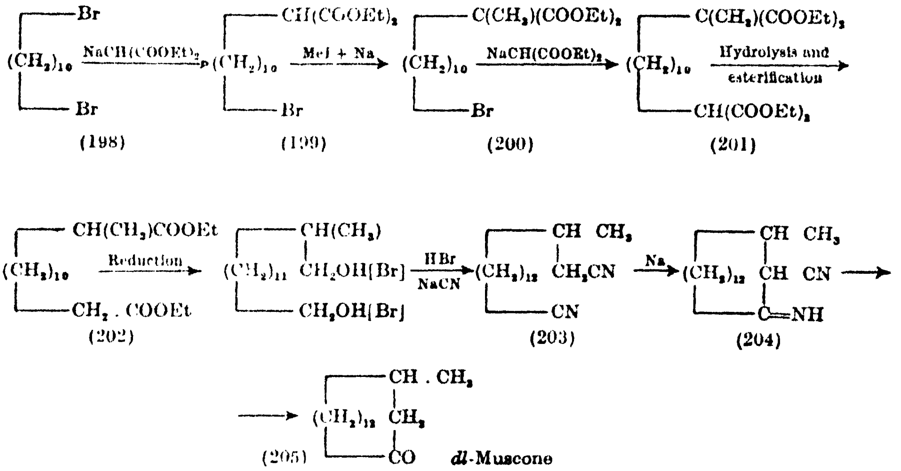
[1] Hunsdiecker, *Ber.*, 1943, **76B**, 142.

Finally, *dl*-muscone was synthesised by Ziegler and Weber,[1] and by Ruzicka and Stoll.[2] The elegant method of the former workers is outlined in the formulæ below. The starting point is 1, 10-dibromodecane (198) which, when allowed to react with sodiomalonic ester under restricted conditions, gives the 'half ester' (199) or 10-bromodecylmalonic ester. By the familiar methods



a methyl group is introduced into the malonic group (200), after which the second bromine atom is caused to react with sodiomalonic ester, giving the tetracarboxylic ester (201). This, after hydrolysis and re-esterification, yields terdecane-1, 12 dicarboxylic ester (202) which, after successive reduction, treatment with hydrobromic acid and with sodium cyanide, yields methyl tetradecane dicyanide (203). The dicyanide is cyclised to *dl*-muscone (205) *via* the imino-nitrile (204).

Reference has been made to the formation of a series of cyclic ring ketones by the action of heat on the thorium salts of appropriate dibasic acids. The yields are often quite small, and the success of the investigations depended to a considerable extent on the provision of adequate supplies of dibasic acids with carbon numbers from eleven upwards. The details of this aspect of the research were patiently worked out by Chuit[3] and his collaborators.[4] The main reactions used are illustrated in Table XX, in which the principal stages are labelled A, B and C. These letters connote the same stages in Table XXI, where the progress of these reactions is summarised, showing the formation of the full series of dibasic acids.

It will readily be realised that in proceeding from azelaic acid to, say, pentadecane dicarboxylic acid, ten steps are involved. If the yield at each stage averages 80 per cent. each gram of azelaic acid will yield $(0{\cdot}8)^{10}$ or 0·1 gm. of final product; if the average yield is only 66 per cent., the final yield is 0·02 per gm. of raw material. In cyclising this acid via the thorium salt the yield

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[1] Ziegler and Weber, *Ann.*, 1934, **512**, 164.

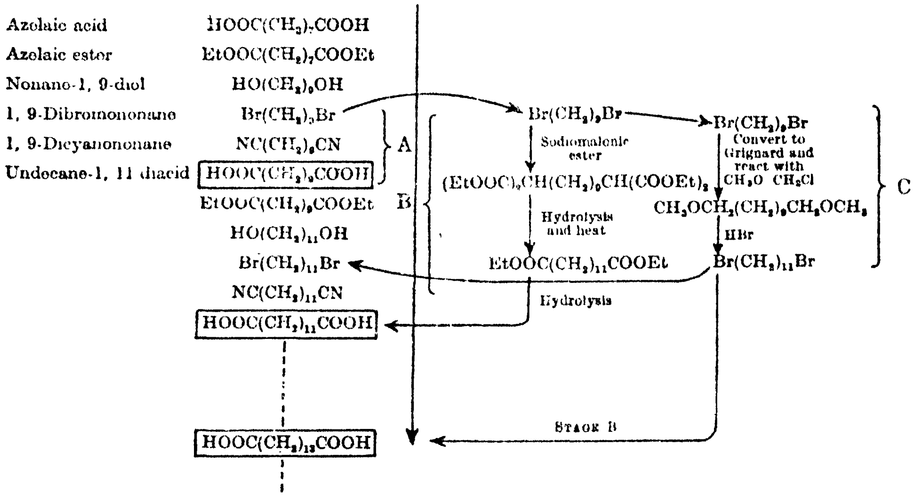
[2] Ruzicka and Stoll, *Helv. Chim. Acta*, 1934, **17**, 1308.

[3] Chuit, *ibid.*, 1926, **9**, 264.

[4] Chuit and Malet, *ibid.*, 1926, **9**, 1074.

TABLE XX

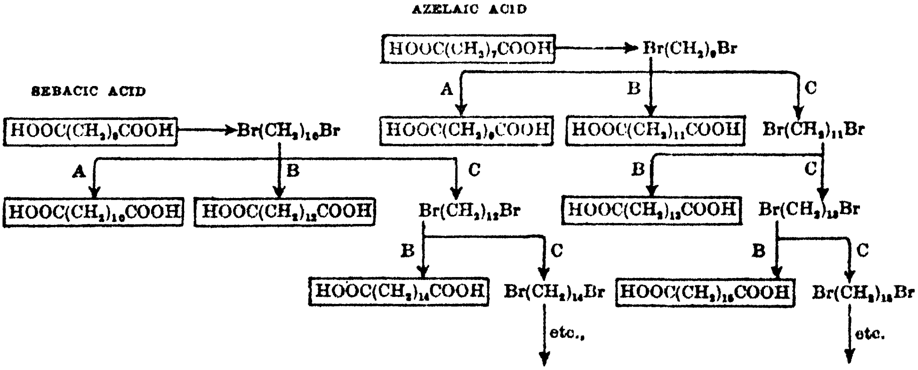
FORMATION OF HOMOLOGOUS DIBASIC ACIDS


Azelaic acid $HOOC(CH_2)_7COOH$
Azelaic ester $EtOOC(CH_2)_7COOEt$
Nonane-1, 9-diol $HO(CH_2)_9OH$
1, 9-Dibromononane $Br(CH_2)_9Br$
1, 9-Dicyanononane $NC(CH_2)_9CN$
Undecane-1, 11 diacid $HOOC(CH_2)_9COOH$
$EtOOC(CH_2)_9COOEt$
$HO(CH_2)_{11}OH$
$Br(CH_2)_{11}Br$
$NC(CH_2)_{11}CN$
$HOOC(CH_2)_{11}COOH$
$HOOC(CH_2)_{13}COOH$
A
B
$Br(CH_2)_9Br$
Sodiomalonic ester
$(EtOOC)_2CH(CH_2)_9CH(COOEt)_2$
Hydrolysis and heat
$EtOOC(CH_2)_{11}COOEt$
Hydrolysis
$Br(CH_2)_9Br$
Convert to Grignard and react with
$CH_3O\ CH_2Cl$
$CH_3OCH_2(CH_2)_9CH_2OCH_3$
HBr
$Br(CH_2)_{11}Br$
C
Stage B

is only 0·2 per cent., consequently the overall yield from azelaic acid is between 0·02 and 0·004 per cent. In terms of actual material this means that the earlier investigators had to transform 5–25 kg. of azelaic acid in order to produce 1 gm. of *cyclo*hexadecanone.

TABLE XXI

FORMATION OF HOMOLOGOUS DIBASIC ACIDS



APPENDIX II

PLASTICS

During the latter portion of last century, when organic chemistry was growing at an enormous rate, it was a matter for profound disappointment when a reaction calculated to produce a " beautifully crystalline compound " gave only a resinous mass. The usual fate of such apparently unsuccessful experiments was the waste-box, since the time had not yet come when such resins could be successfully employed as raw materials for construction.

There are hints in the work of Baeyer, when about 1872 he was experimenting on the interaction of aldehydes and phenols, that the resins he so frequently obtained might, at some future time, have a useful application; but it remained for Trillat, in 1896, to discover the thermo-setting properties of phenol-formaldehyde resins, and to exhibit the resins themselves at the Paris Exposition of 1900. Trillat had observed the formation of a liquid resin when phenol and formaldehyde react, and showed that on further heating it could be irreversibly converted to an insoluble material. His main hope was that the new resin might supplement or replace camphor in the manufacture of celluloid. It will be recalled that celluloid (nitrocellulose, plasticised with camphor) was one of the earliest 'plastics', being moulded into an infinite variety of small articles, combs, toys and the like, which, on account of the extreme, almost explosive, inflammability, had proved dangerous, leading to much loss of life. Although Trillat's products were satisfactory, they did not attract the attention they merited, partly owing to the great cost of formaldehyde (then produced from methanol obtained from wood distillation), and partly owing to difficulties in obtaining sufficient quantities of high-grade phenol. Trillat's work then lapsed into oblivion, until in 1909 Baekeland published his work on the various phases of the phenol-formaldehyde resins and proceeded to develop the industrial aspects of the invention.

Most of the plastics are examples of macromolecular structure, or molecules which are as large as the fragment of material being considered, or, in other words, lattices which extend indefinitely throughout the structure. There are (apart from the rubber-like polymers, which have already been considered) three main groups of plastics :—

(1) *Thermoplastic Resins.*—Materials which, whilst having a tolerably rigid structure at ordinary temperatures, soften on heating, passing through a plastic state during which they can be coerced into any required shape. On cooling they regain their comparative rigidity, but the softening upon application of heat, and the regain of rigidity on cooling are reversible.

(2) *Thermosetting Resins.*—Materials, usually incorporated into powders which, on heating, are irreversibly converted to a rigid form, which does not melt again. This setting process is usually carried out in heated moulds under pressure, so that by using multiple moulds, numerous single articles can be produced by one operation.

(3) *Casein Plastics.*—Materials which occupy a position between the two types previously mentioned.

The choice of a plastic material from the many varieties available depends largely on the purpose to which the material is to be put. Where perfect transmission of light is desired, a choice is limited to certain of the vinyl and methyl methylacrylate types; if insulating properties are desired, polystyrene offers excellent electrical properties, but for purely mechanical strength the thermo-setting resins and their laminates are to be preferred. It is proposed to discuss some of the more valuable plastic materials in some detail.

THERMOPLASTIC RESINS

The cellulose esters and ethers are well-known members of this group. Some of the more common types and applications are shown in Table XXII :—

TABLE XXII

SOME CELLULOSE PLASTICS

Cellulose Acetate.—Used for the preparation of transparent sheets and mouldings, and for the earliest types of safety glass. Its transparency and resistance to discoloration by light are inferior to those of most other transparent plastics, but the ease and cheapness of production is an asset.

Cellulose Acetate/Butyrate.—Slightly lower specific gravity than the acetate; more elastic, but of equivalent compressive strength and hardness.

Methylcellulose.—A fibrous material which swells and gives a tragacanth-like pseudo-solution in water. An adhesive rather than a plastic.

Ethyl Cellulose.—Requires less plasticiser than cellulose acetate, and is thereby less liable to colour deterioration. Has a better transmissibility, dielectric properties and mechanical strength than the acetate, and is replacing it for many purposes.

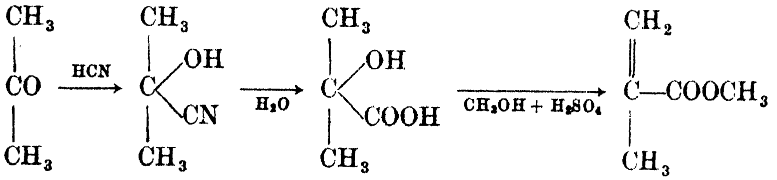
Benzyl Cellulose.—Mainly used as a modifier for injection and compression moulding powders.

Cellulose Nitrate.—When plasticised by camphor, gives the material 'celluloid'. Celluloid may be regarded as the progenitor of the plastic family; it is violently inflammable, and from this standpoint a most dangerous material of construction.

Examples of the great variety of ways in which cellulose esters and ethers are used in plastics and related fields will be well known to most readers. Thin films of the acetate are prepared by continuous film casting, which consists of 'doctoring' on to a suitable roller a film of cellulose acetate solution which evaporates leaving a thin film which is floated from the roller and wound into reels. Such products as "Cellophane" are widely used for wrapping; to render them 'heat sealing' and to some extent water-impervious, they are often coated with a thin film of polyvinyl acetate.

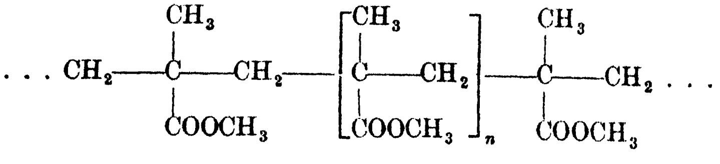
The plastics with the finest optical properties are those derived by the polymerisation of the methyl ester of methyl acrylic acid, the clear massive form of which is known as 'Perspex', whilst a moulding powder is called 'Diakon'.

The raw material for 'Perspex' production is acetone, which is converted to its cyanhydrin, which in turn gives methyl methylacrylate when heated under pressure with methyl alcohol and sulphuric acid at 100–110°. These changes are symbolised :—



$$(CH_3)_2CO \xrightarrow{HCN} (CH_3)_2C(OH)CN \xrightarrow{H_2O} (CH_3)_2C(OH)COOH \xrightarrow{CH_3OH + H_2SO_4} CH_2{=}C(CH_3){-}COOCH_3$$

When methyl methylacrylate is heated to 190° a clear glass-like plastic is obtained, of which the structural unit appears to be



$$\ldots CH_2-\underset{COOCH_3}{\overset{CH_3}{C}}-CH_2-\left[\underset{COOCH_3}{\overset{CH_3}{C}}-CH_2\right]_n-\underset{COOCH_3}{\overset{CH_3}{C}}-CH_2\ldots$$

Sheets and rods of 'Perspex' can be cut, sawn and drilled with ease; the material appears to be almost unaffected by light, and shows no discoloration after long periods of irradiation. It is unaffected by water, has optical uniformity (i.e. does not distort the field of view due to irregular refractive index), and has a light transmissibility in the visible which is superior to that of glass. Thus, it is eminently suitable for the moulding of lenses which are virtually 'unbreakable'. The only drawback to its use in this capacity is that it is more easily scratched than is glass. It has been widely used for nosepieces, cockpit enclosures, domes, etc., in aircraft construction.

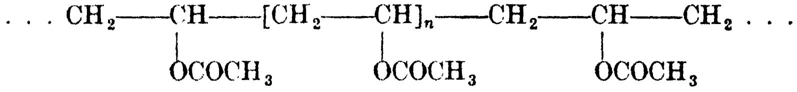
Vinyl Types.—When vinyl chloride is polymerised, the simple unit

$$\ldots CH_2{-}CH(Cl)[CH_2{-}CH(Cl)]_nCH_2{-}CH(Cl) \ldots$$

is obtained, the product usually being designated by the letters P.V.C. The material, polyvinyl chloride, is of particular interest for sheathing wires and cables on account of its good electrical properties, resistance to wear, low water absorption, and its flexibility over a wide temperature range. The thermoplastic properties of P.V.C. allow of its application to wire by an extrusion press. The properties of P.V.C. can be altered a little by controlling the degree of polymerisation; the advantage gained by using a slightly arrested polymerisation (as in " Welvics ") is increased flexibility at low temperatures.

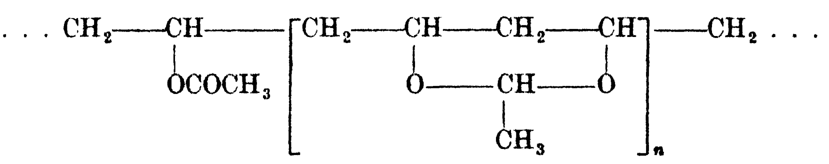
Many special types of plastic are obtained by co-polymerising vinyl chloride with other monomers such as vinyl acetate, aldehydes, etc., to obtain co-polymers of widely different types. The main advantages of co-polymerisation is that the product retains the good properties of both individual polymers; co-polymers of vinyl chloride and vinyl acetate are mechanically strong, very resistant to chemical attack, and are capable of being moulded from the powder form.

Vinyl acetate polymerises readily to clear transparent plastics, which are low in melting point, and of little mechanical strength. The production of vinyl acetate is described on page 111, and during polymerisation it gives the unit :—



$$\ldots CH_2{-}\underset{OCOCH_3}{\underset{|}{CH}}{-}[CH_2{-}\underset{OCOCH_3}{\underset{|}{CH}}]_n{-}CH_2{-}\underset{OCOCH_3}{\underset{|}{CH}}{-}CH_2 \ldots$$

Enormous increases in strength of such resins are brought about if polyvinyl acetate is partly hydrolysed to polyvinyl alcohol and allowed to react with aldehydes—usually acetaldehyde or *n*-butyraldehyde. Acetals are formed of the unit structure :—



POLYVINYLACETAL

These resins have a very high light transmissibility in thin films, coupled with great strength, and are used for the inner layer of ' safety-glass ', and for a bonding material in the manufacture of laminated plywood.

One of the most important groups of synthetic plastics from the standpoint of chemical work are those known as the ' Sarans '. They are vinylidene chloride polymers of which the unit is

$$\ldots CH_2{-}CCl_2{-}[CH_2{-}CCl_2]_nCH_2{-}CCl_2 \ldots$$

This plastic is almost completely unaffected by water, stands the effects of many chemicals, is tough and uninfluenced by bending. Tubes 5/16 in. O.D. and 3/16 in. I.D. made of ' Saran ' were subjected to a fatigue test by being flexed through a 15° arc at the rate of 1750 times a minute. After 2½ million bends, the tube was still intact, whereas an ordinary copper pipe of the same dimensions fractured after 500 cycles. It is eminently suited to the construction of chemical plant, both as tubes and for tank linings. The fact that it is odourless, non-inflammable, and very resistant to abrasion are added advantages.

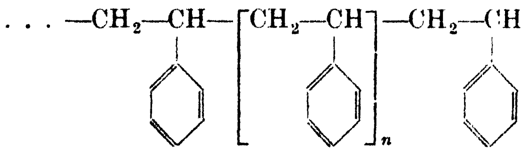
There are certain peculiar features characteristic of the 'Saran' plastics; when first produced and extruded it is soft and mechanically weak, but on standing it goes through a stage of 'age-hardening' during which it undergoes oriented crystallisation, and becomes hard. If stretched during age-hardening, it becomes exceedingly strong, with a breaking tensile of 60,000 lb. per sq. in. This plastic offers great possibilities for future developments in chemical engineering.

Hydrocarbon Plastics

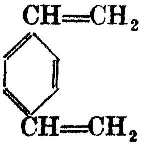
Polythene, a polymerised ethylene sold in this country under the trade name "Alkathene", is probably one of the most inert chemical substances in this field. It is soft and without marked mechanical strength, but is possessed of such a marked resistance to concentrated hydrochloric and nitric acid, and to 50 per cent. caustic soda as to merit the proper application of the name "paraffin"; indeed, in many ways polythene appears to correspond to the macromolecular paraffin obtained by indefinite propagation of the methylene group. Although not fully transparent polythene transmits light, and although it is not wetted by water it is not impervious to water vapour, which can diffuse through it. Polythene will burn, but only slowly; it is also unaffected by prolonged exposure to ozone.

The use of polythene is indicated where films or tubes of definite elasticity, high dielectric properties and general resistance to chemical attack are desired.

Other hydrocarbons are capable of polymerisation, but the products are largely elastic, rather than plastic, and are discussed in Chapter III (see pp. 200 ff.). An exception is polystyrene, obtained by the controlled polymerisation of styrene, of which the structural unit is



In most industrial polystyrene resins the hardness and insolubility in organic solvents have been increased by cross-linkages due to the incorporation of a little divinyl benzene (206) in the original styrene; with 1 per cent. the insolubility in organic solvents is complete. The effect on the structure is, probably, that shown in (207)



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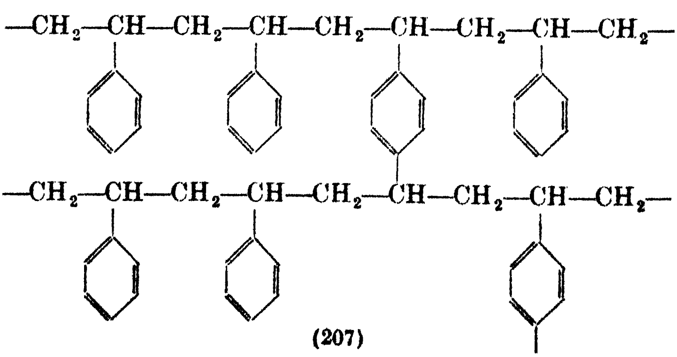


(207)

TABLE XXIII

Physical Properties of some Thermoplastics

Property	Polythene	Methyl methyl-acrylate polymer	Polystyrene	Vinylidene chloride polymer	Polyvinyl Butyral	Polyvinyl acetal	Polyvinyl Copolymer	Polyvinyl chloride	Ethyl cellulose	Nitrated cellulose	Cellulose acetate/butyrate
Tensile strength [lb. per sq. in.] .	low	7500–8000	6000–7000	up to 60,000	7000	8000–11,000	8000–10,000	3500–4000	4000–8000	3000–8000	2500–9900
Elongation, per cent.	high	—	1	25	—	—	—	130–200	—	—	5–90
Mod. elasticity $\times 10^{-5}$ [lb. per sq. in.] .	—	4·5	4·5–5·0	—	—	4–10	5–6	3–4	2–4	2–4	2–3·5
Hardness Brinell [2·5 mm. ball. 25 kg. load] .	scarcely measurable	18–20	20–30	65–95	—	12–16	15–25	low	5–10	8–11	6–12
Surface resistance [megohms $\times 10^{-6}$/sq. cm.] . .	10^2	—	10^4	—	—	—	—	—	—	—	—
Volume resistance [megohms $\times 10^{-6}$/cu. cm.] . .	10^5	10^3	10^5–10^7	60	100	—	—	1–40	—	0·1–0·3	0·7–1·4
Breakdown value [volts/mil.] .	1000	390	500–700	500–2500	—	—	400–500	250–350	1500	600–1200	350–900
Resistance to water	perfect	good	perfect	perfect	good	moderate	good	good	good	good	good
Dielectric constant .	2·3	—	2·6–2·7	3–5	3·6	—	4	—	2·5–3·7	6·7–7·5	3·5–6·4
Specific gravity .	0·92–0·94	1·19	1·05–1·07	1·6–1·75	1·1–1·2	1·2–1·4	1·3–1·4	1·35–1·4	1·2	1·3–1·8	1·15–1·4
Trade Name	'Alkathene'	'Perspex' 'Diakon'	'Distrene'	'Saran'	'Butacite'	'Bexone'	'B.X.P.V.C.'	'Welvic'	Ethyl cellulose	(Sheet) 'Xylonite'	'Tenite'

Injection mouldings of polystyrene are transparent, and have a moderately good transmissibility for light; it has the power of transmitting light through curved rods. Polystyrene has many properties which recommend its use in the construction of transparent aircraft parts, namely, ability to retain its impact strength at low temperatures, dielectric properties comparable to those of mica and, for a plastic, a relatively high Young's Modulus, giving objects constructed from it considerable dimensional stability under stress.

It is not proper to leave this group of plastics without some discussion of the group of plastic filaments to which the term "Nylon" has been applied. In 1935 Carothers synthesised an anhydride in which the units were alternating molecules of adipic acid, and hexamethylene diamine; the structural unit of the "Nylon" chain is

$$\ldots\ \mathrm{NH(CH_2)_6NH[CO(CH_2)_4CO\,.\,NH(CH_2)_6NH\,.]_n}$$
$$\mathrm{CO(CH_2)_4CO\,.\,NH(CH_2)_6NH}\ \ldots$$

This material, which has an apparent molecular weight of 10,000 and melts at 263°, gave threads when melted and drawn which are brittle, but which, on being stretched to several times their original length, become extremely elastic, and can be knotted, spun and woven with the greatest of ease. The fact that "Nylon" is not affected by water, and cannot absorb more than a trace of water, make it unique amongst textile fibres, as it is unaffected by washing, can be dried after wetting in a few moments, and is not liable to the ordinary shrinkage troubles. Indeed, its inability to absorb much moisture, becomes a drawback to the use of fabrics woven from it, since they are cold to the touch, and are incapable of absorbing respiratory water-vapour, as wool does.

The toughness of the individual "Nylon" fibres and the ease with which fabrics made from them can be 'set' to shape by heat treatment has already made a revolution in the hosiery industry. It has also caused a dearth of phenol, since both raw materials for its production are made from phenol, through *cyclo*hexanol, adipic acid and adipamide.

The physical properties of some of the more important thermoplastics are shown in Table XXIII.

THERMOSETTING PLASTICS

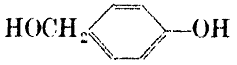
It is not possible to give a detailed account of all the various types of thermosetting resins within the scope of this Appendix; whereas the thermoplastic resins fall within a fairly small group of relatively unmodified compounds (e.g. methyl methylacrylate is usually polymerised as the pure compound), the thermosetting plastics are compounded with a wide variety of fillers, plasticisers, modifiers, colours and other components that, even starting with the simple phenol-formaldehyde base (P.F. base), there is a wide variety of final products, covering a wide range of physical properties.

If a phenol-formaldehyde moulding be made from the usual P.F. base without fillers, etc., it has little mechanical strength, and is too brittle for use. Fillers such as wood flour, dried paper pulp, cotton flock, silica, or even disintegrated oat-hulls, are incorporated in proportions up to 20 per cent. and vastly increase the strength and utility of the moulding. Again, the thermosetting resins may be used to bond laminates—which are essentially plastics with an oriented filler; layers of paper, cloth or glass fabric can be used, and extremely tough products result. For example, if layers of glass fibre cloth are impregnated with a P.F. base and cured under pressure (preferably by high frequency heating), a laminate is obtained which has a tensile strength of up to 250 tons per sq. in.; that is, equal to the finest piano-wire steel, but at half the weight. When woven fabric bases are used, laminates are obtained which have excellent mechanical and machining properties, and can be used for gear-wheels, where their resistance to wear is superior to that of mild steel ("Tufnol"). Such pinions make far less noise than steel gears and are, therefore, a valuable contribution to silent-running plant. From the few remarks in these two paragraphs it will be seen that the production and utilisation of thermosetting plastics is an intricate art, existing independently of the chemistry of the subject.

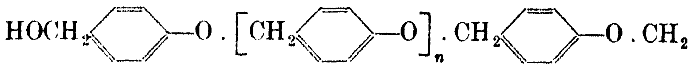
The main thermosetting plastics are

(1) Phenol-formaldehyde (P.F.) compositions.
(2) Urea-formaldehyde resins.
(3) Phenol-furaldehyde resins.
(4) Melamine resins.
(5) Glycerol-phthalic anhydride resins.

Much research has been directed towards ascertaining the precise arrangement of atoms and groups in the thermosetting plastics ; the general conclusion is that the first stage is the condensation of phenol and formaldehyde to form a



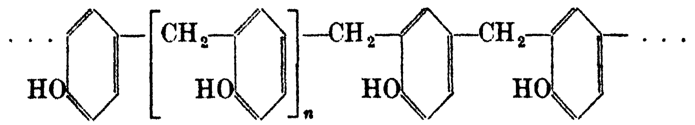
(228)



(229)

di-functional molecule (228), *p*-hydroxybenzyl alcohol, and that this by reacting with further molecules of formaldehyde and phenol can give a linear polymer of the type shown in (229), when the reaction is allowed to take place in the presence of a trace of acid. The elimination of water is shown by the separation of the reaction mixture into two layers, one aqueous and the other consisting of the liquid resin. These low polymerised liquid resins are insoluble in alkali, showing that the phenolic function has disappeared during their formation ; they are soluble in a number of organic solvents.

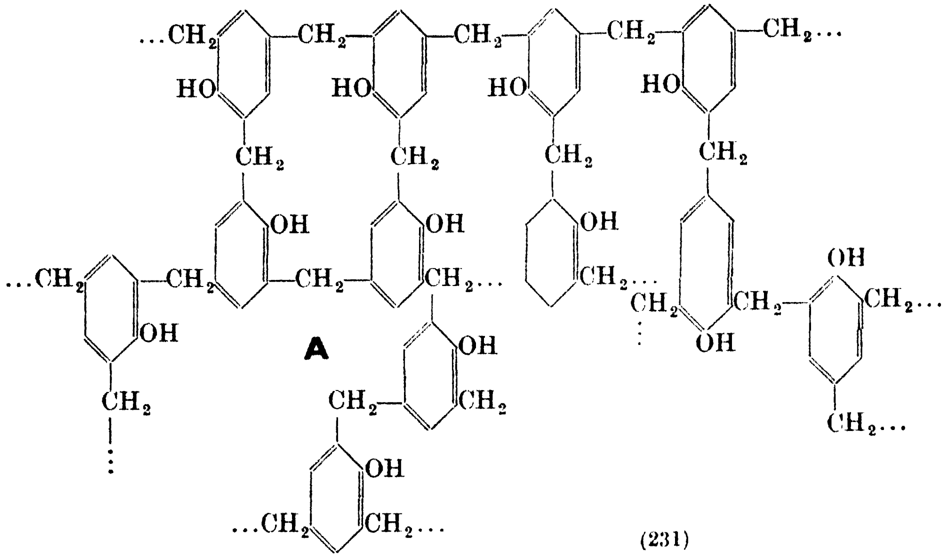
The further polymerisation of these liquid resins is characterised by two stages, the formation of a solid resin which still retains its solubility in acetone and the further polymerisation to a solid which is insoluble in acetone. From the chemical standpoint, it is by no means clear that the lower polymers of the type (229) give higher polymers by the same type of linkage as that by which they themselves were formed. To appreciate this point it is necessary to consider the type of compound which is obtained by the action of alkaline catalysts upon mixtures of phenol and formaldehyde. In these cases the lower polymers retain both their solubilities in alkalies and in organic solvents, and structures such as (230) are common.



(230)

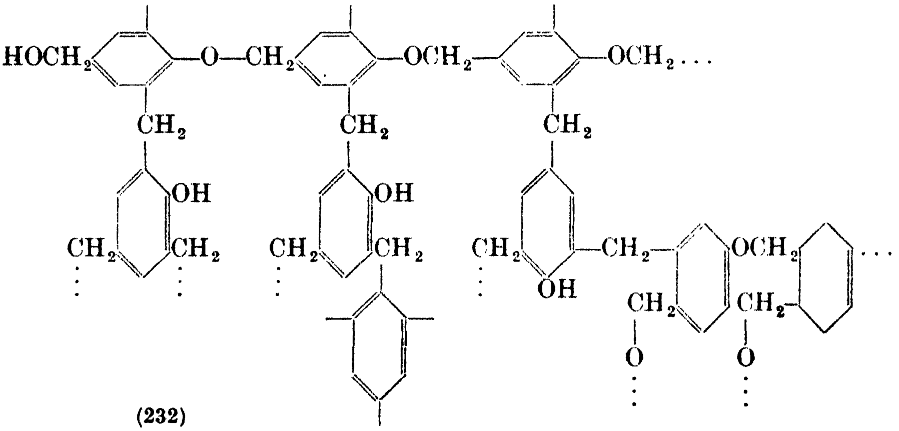
As polymerisation proceeds, a three-dimensional macro-molecule is built up in which the positions *ortho-* to the hydroxyl group are fully occupied, as in the structure (231). This structure is merely a diagram to illustrate the manner in which the macro-molecule may be constituted ; as shown at '**A**', the formation need not necessarily be considered as indefinitely arborescent, but may have a limited number of additional ring-forms.

Reverting now to the simple acid-formed polymer (229), this can undoubtedly give a higher polymer, as indicated in (232), whilst the alkali-formed polymer may give links as shown in the type-molecule (233). In practice, a mixture of all these types probably occurs in industrial polymers, and the variations in



(231)

properties experienced as a result of the alterations in catalyst and in curing technique, are probably due in a large measure to the influence of these details on the proportions of different types of linkage present.



(232)

By substituting a proportion of the phenol in such resins by cresols and xylenols with a restricted capacity of *ortho*- condensation, resins are obtained which dissolve in oil and give excellent varnish bases.[1]

Amines can also replace phenols in making polymers with formaldehyde, and it is considered that they contain similar structures.[2]

Resins obtained with m-***phenylene diamine*** and certain other amines are able to exercise base-exchange functions similar to those of zeolites, and can remove traces of iron, for example, from water.[3] This is of considerable value in the dyeing industry. A similar principle has been used for concentrating organic biological substances from aqueous solutions containing them in small proportion.

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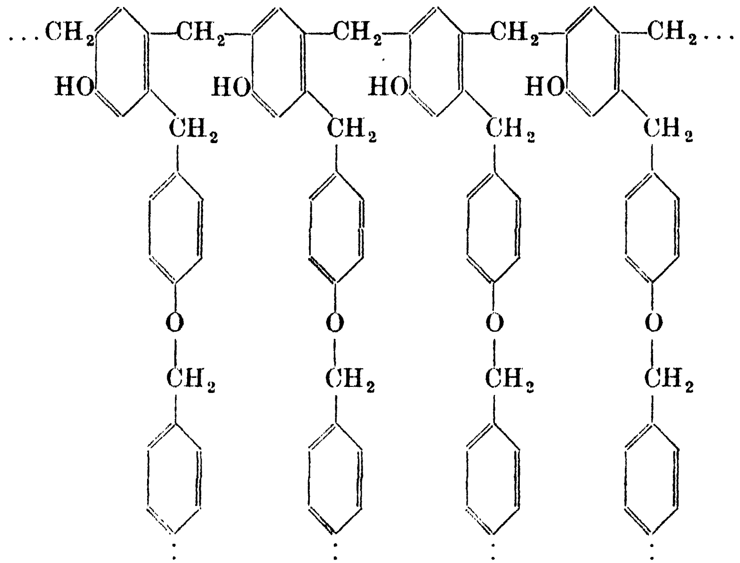
[1] Turkington and Allen, *Ind. Eng. Chem.*, 1941, **33**, 966.

[2] Spring, *Chem. Rev.*, 1940, **26**, 297.

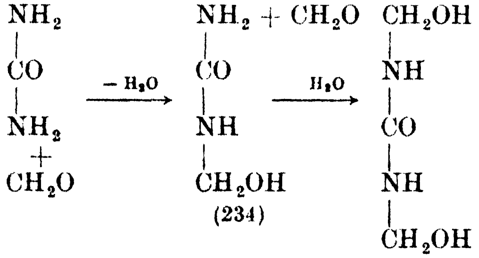
[3] Adams and Holmes, *J.S.C.I.*, 1935, **54T**, 1.



(233)

Urea-formaldehyde Resins.—One disadvantage of P.F. resins is their dark colour ; urea-formaldehyde resins are of a very light colour, and, moreover, are without the faint odour associated with the P.F. type.

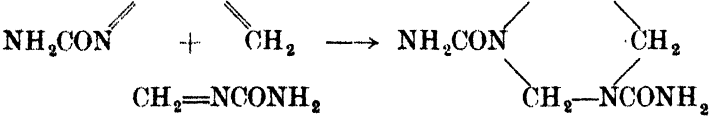
The first stages in urea-formaldehyde condensation give methylol urea (234) and dimethylol urea (235).



$$NH_2{-}CO{-}NH_2 + CH_2O \xrightarrow{-H_2O} NH_2{-}CO{-}NH{-}CH_2OH \;(234) \;+\; CH_2O \xrightarrow{H_2O} CH_2OH{-}NH{-}CO{-}NH{-}CH_2OH \;(235)$$

Either of these products can give irreversible polymer formation on heating. Usually they are incorporated with fillers and dyestuffs, and are often impregnated into timber before polymerisation.

Little is known as to the precise structure of U.F. resins ; they may consist of cross-linked polymers analogous to the P.F. series ; but suggestions have been made that methylene urea (236) is formed by the dehydration of methylol urea, and that this gives a trimer (236), which is capable of further condensation



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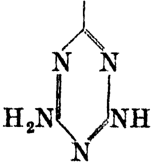


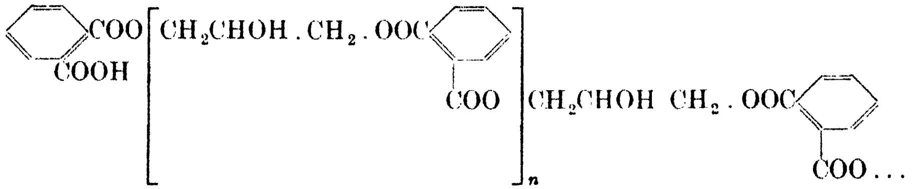
(238)

to mixed cyclic/linear resins. U.F. resins are frequently encountered under the trade name ' Beetle '.

If the cyclic structure for U.F. resins be correct, then their structure will show an analogy with the *Melamine Resins* (or M.F. resins) obtained by the condensation of melamine (134) with formaldehyde. The great stability of these resins to the effects of heat, light and water and their high mechanical strength is making them valuable additions to the family of plastics.

GLYCEROL-PHTHALIC ANHYDRIDE RESINS (GLYPTALS)

These resins (also known as " alkyd " resins) are a valuable series of bonding agents for mica, asbestos, and for the insulation of electrical windings. They have the advantage of withstanding heat when cured, and of readily penetrating the solid filler or laminæ when still in the liquid state. Glycerol is most commonly used as the hydroxylic component, although the formation of resins is not specifically restricted to glycerol; for special types of alkyd resins glycol, mannitol or sorbitol are used. The first stage in the formation of glyptals is the formation of a linear polymer of the general type (239); this, on resin formation yields a cross-linked macro-molecule of the type shown in structure (240). The formation of these polymers is more fully discussed from the theoretical standpoint in Vol. III.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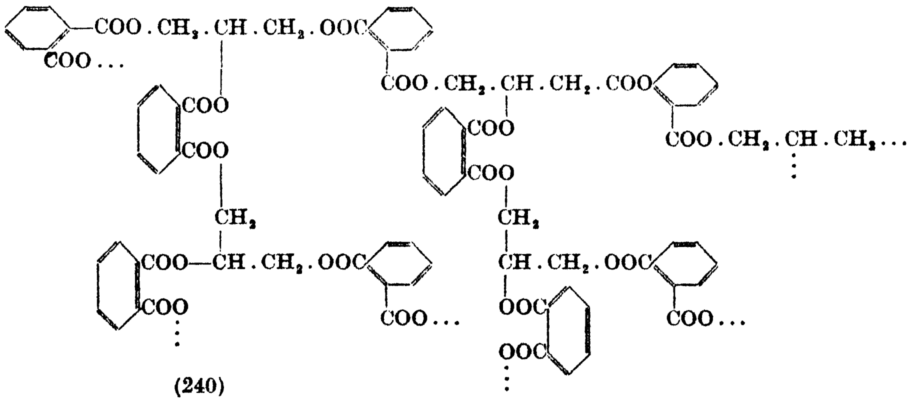
(240)

Silicones.—Although the silicones are not entirely " organic " compounds, they form plastics which are of interest to organic chemists. At the commencement of the century Kipping, at Nottingham, began [1] a series of researches on the organo-silicon compounds, which had for their general purpose the elucidation of stereochemical problems related to the silicon atom, and an examination of the nature of compounds in which silicon had wholly, or partly, replaced the carbon. This series of researches has been pursued over nearly half a century and has resulted in a monumental series of publications to which further reference is made in Vol. II. in the chapter entitled " Heteroid Organic

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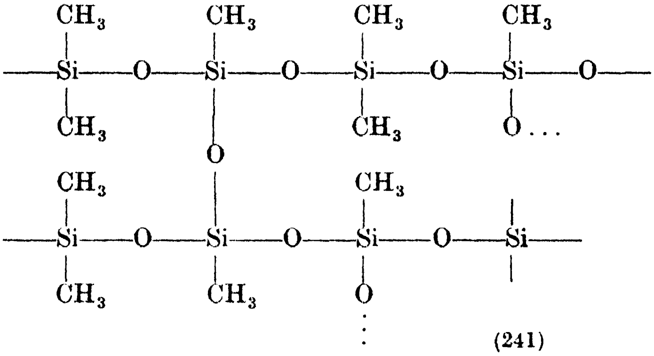
[1] Kipping and Lloyd, *J.C.S.*, 1901, **79**, 449.

Compounds". Among the many compounds discovered and examined by Kipping and his co-workers were two groups :—

(*a*) The silicane diols, $R_2Si(OH)_2$
(*b*) The silicane triols, $RSi(OH)_3$

both of which were shown to be capable of polymerisation. In 1941, Rochow and Gilliam [1] showed that co-polymerisation of the silicane diols and triols (where $R = CH_3$) gave a resinous polymer, which could be obtained in both liquid and solid forms. The structure of a cross-linked siloxane (241) is suggested for these resins, similar to that given by Adrianov [2] for the polymers obtained by partial hydrolysis of the alkyl substituted silicon esters. Silicones can be used as sheathing for wire and cable, and are unchanged by exposure to a temperature of 200° for a year ; the electrical properties are good, so that the use of silicone insulated windings in motors not only decreases the fire and corrosion risks, but allows of using a smaller motor for a given horse-power. Liquid silicones have great stability, and an almost immeasurable vapour pressure, and are valuable stopcock lubricants and as media for high-vacuum vapour pumps.



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APPENDIX III

ORGANIC PHOTOSYNTHESIS

That vegetable organisms imbibe water, inspire carbon dioxide, and elaborate carbohydrates from these raw materials is a truism ; the mechanism by which this process takes place, and the possibility of achieving the same end *in vitro* have been hotly debated.

It is clear that there is no simple mechanism by which, for example, the reaction :—

$$6CO_2 + 6H_2O + 673{,}000 \text{ calories} \longrightarrow C_6H_{12}O_6 + 6O_2$$

can be accomplished, and quite early in the history of this subject, Baeyer,[3] in 1870, suggested that formaldehyde is the key intermediate. As it was known, even then, that formaldehyde could readily be induced to form mixtures of hexose sugars (α-acrose) in the presence of water and of traces of alkalies, it apparently only remained to demonstrate the formation of formaldehyde itself in the plant.

Usher and Priestley,[4] in 1911, irradiated a pure aqueous solution of carbon dioxide with ultraviolet light from a mercury in quartz lamp. They obtained solutions which gave a positive reaction for formaldehyde when tested by Schryver's reagent. Various attempts to repeat this work [1] gave negative results; later, Moore and Webster [2] obtained positive evidence of the formation of formaldehyde by irradiation of sealed tubes containing an aqueous solution of carbon dioxide in which had been suspended a trace of colloidal ferric or uranium hydroxide. These investigators used direct sunlight for their experiments. Again, Spoehr and others failed to find corrobative evidence, and were unable successfully to repeat Moore and Webster's experiments. Baly, Heilbron and Barker [3] took conductivity water, and after saturation with carbon dioxide irradiated the solution in quartz tubes; no formaldehyde could be detected, while the reaction mixture was static, but in tubes where a constant current of carbon dioxide was passed, the solution gave positive tests for formaldehyde. These investigators took the viewpoint that Moore and Webster obtained positive results not because their metallic sols catalysed the reaction $H_2CO_3 \longrightarrow CH_2O + O_2$, but because such substances prevented the decomposition of formaldehyde, or its transformation to more complex compounds. Porter and Ramsperger [4] were unable to repeat the work of Baly and his co-workers, and were inclined to attribute their positive results to contamination with traces of organic material from rubber connexions or stopcock grease. It must, however, be pointed out that their results were not obtained by an *exact* repetition of the English workers' experiments, and Baly rightly contended that they had omitted the use of a continual stream of carbon dioxide which in his opinion was the vital factor, inasmuch as it was only in such experiments as had included such a stream of gas that positive reactions for formaldehyde had been obtained.

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[1] Rochow and Gilliam, *J.A.C.S.*, 1941, **63**, 798.
[2] Adrianov *et al.*, *Org. Chem. Ind. U.S.S.R.*, 1939, **6**, 203.
[3] Baeyer, *Ber.*, 1870, **3**, 63.
[4] Usher and Priestley, *Proc. Roy. Soc.*, 1911, **84B**, 101.

It will have been noted that the quantities of formaldehyde produced, if any, are exceedingly small, and it is necessary to ask

(*a*) Whether the substances which give the positive reaction with Schryver's reagent are really formaldehyde, and

(*b*) If the answer to (*a*) is affirmative, is the formaldehyde produced by the irradiation of carbon dioxide and water?

Schryver's test is carried out [5] by adding 2 ml. of a freshly prepared solution of phenylhydrazine hydrochloride (2 per cent. strength; freshly filtered) to 10 ml. of the solution to be examined. This is followed by 1 ml. of a recently made solution of potassium ferricyanide (5 per cent. strength). The presence of formaldehyde is then recognised by the formation of a bright red colour on the addition of concentrated hydrochloric acid (5 ml.). One part of formaldehyde in a million of water can be recognised in this way.

The test appears to be specific for formaldehyde, so that the answer to question (*a*) above, is in the affirmative. The next question cannot be easily answered; the possibilities are

(i) That the formaldehyde detected by Baly and his co-workers arises from contamination.

(ii) That it is formed indirectly from CO_2 and water through the intermediate production of a more complex substance X, thus

$$CO_2 + H_2O \longrightarrow X + O_2 \longrightarrow CH_2O + O_2$$

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[1] Spoehr, *Biochem. Zeitschr.*, 1913, **57**, 110.

[2] Moore and Webster, *Proc. Roy. Soc.*, 1914, **87B**, 163.

[3] Baly, Heilbron and Barker, *J.C.S.*, 1921, **119**, 1025.

[4] Porter and Ramsperger, *J.A.C.S.*, 1925, **47**, 79.

[5] Schryver, *Proc. Roy. Soc.*, 1910, **82B**, 226.

(iii) That it is formed directly by the irradiation of the carbon dioxide solution

$$CO_2 + H_2O \rightleftarrows CH_2O + O_2$$

The balance of evidence points to the conclusion that the third alternative is true, namely, that under proper conditions minute traces of formaldehyde are formed by irradiating aqueous solutions of carbon dioxide. It may also be added that the difficulty of detecting such quantities of formaldehyde lies in the fact that the photostationary state lies well over on the $CO_2 + H_2O$ side, and that the formaldehyde is readily transformed into other and more complex substances.

The second part of this investigation involved proof that formaldehyde can be converted into sugars, and even more complex carbohydrates. Of this there is no doubt; Baly and his co-workers obtained ample evidence that reducing sugars are formed when continually neutralised solutions of formaldehyde are exposed to ultra-violet irradiation. That these sugars are not always those obtained in plant syntheses is scarcely to be wondered at having regard to the differences of the conditions under which the reactions are achieved.

Having settled these points, the following fresh questions have next to be considered:—

(*c*) Can carbohydrates be synthesised *in vitro directly* from carbon dioxide and water?

(*d*) What evidence is there that sugars and other carbohydrates are synthesised in the leaves of plants by methods analogous to those observed *in vitro*?

The answer to (*c*) cannot be explicit; if by 'directly' is meant "without the intermediate formation of formaldehyde", there is evidence to show that starch-like products are formed during the irradiation of solutions of carbonic acid in which is suspended a catalyst consisting of nickel/thorium oxide supported on kieselguhr, but no evidence is adduced that formaldehyde is an inevitable intermediate stage. On the contrary, there is certain evidence which makes it quite clear that many organic compounds, even α-chlorophyll itself, yield formaldehyde when irradiated in the presence of water, but in absence of carbon dioxide. This may mean that even in *in vitro* experiments, formaldehyde is not necessarily an intermediate in carbohydrate synthesis, but only appears as a degradation product. In this connexion, it is proper to point out that there is not yet any evidence available to show that biogenetic synthesis occurs other than by stepwise sequence of reactions; if this be so, then rejection of the hypothesis that formaldehyde is the first step in carbohydrate synthesis *in vivo* is bound up with the necessity of postulating some other simple reaction product formed directly from carbon dioxide and water and capable of furnishing carbohydrates by further elaboration.

Question (*d*) above is, perhaps, the most difficult of all to deal with. There is, clearly, no obvious reason why the chloroplast and leaf system of the plant should use a method of synthesis analogous to that studied by Baly and his co-workers; it is true that the raw materials and end-products are similar; it is likewise abundantly true that minute traces of formaldehyde are demonstrably present in growing plants,[1] and that the dimedon condensation product can be isolated from plant tissues. It is likewise true that formaldehyde is toxic to plants, except in minute traces, and it must, therefore, be almost instantaneously converted to carbohydrate, if formed by photosynthesis.

The problem is rather analogous to an attempt to prove that since it is known that a certain individual was in Manchester on Monday and in London on Friday, he must have travelled by train and have passed through Crewe.

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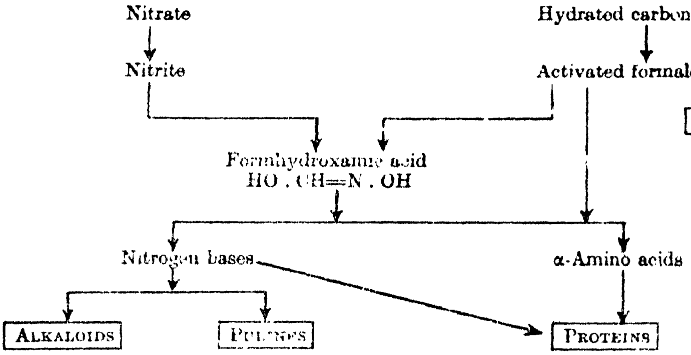
[1] Klein and Werner, *Biochem. Z.*, 1926, **168**, 361.

It is probable that the availability of heavy carbon, C_{13}, will enable some progress to be made with this problem, by labelling the carbon dioxide and following its distribution in the plant.

Baly and his co-workers have given considerable time to the study of the condensation products formed when ammoniacal solutions of formaldehyde are irradiated. They were able to isolate and identify numerous nitrogen bases of the pyridine, pyrole and iminazole series, and as a result of their observations have postulated the formation of the main groups of plant products by the steps set out in the table below :—

TABLE XXIII

BALY'S SCHEME OF PHYTOSYNTHESIS



It must be admitted that only the fringe of this wide and important subject has been studied in detail, and that much yet remains to be done, both in discovering the precise steps by which the complex compounds, which abound in the vegetable kingdom are built up, and in obtaining similar synthesis *in vitro*.

APPENDIX IV

LITERATURE REFERENCES

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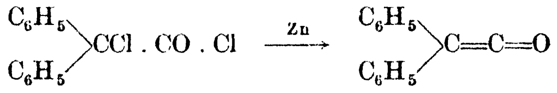
(Much interesting information on plastics is obtainable from " The British Plastics Yearbook ", annual publication of which was commenced in 1938 by the Plastics Press Ltd., London.)

CHAPTER VII

KETENS AND POLYKETIDES

The first representative of the keten family to be prepared was diphenylketen, obtained by Staudinger [1] in 1905 by the action of zinc filings on chlorodiphenylacetyl chloride :—



$$\left.\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\right\rangle CCl\,.\,CO\,.\,Cl \xrightarrow{Zn} \left.\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\right\rangle C{=}C{=}O$$

This substance, a liquid, freezing at about $-10°$ to a yellow crystalline body, shows many of the characteristic keten reactions and served to direct attention to the group. Two years later, in 1907, Wilsmore and Stewart [2] discovered that keten itself, CH_2CO, could be produced by the decomposition of acetic anhydride by an electrically heated platinum spiral.

The pyrolysis of acetone has proved the most convenient and economical method for producing keten, but the method is peculiar to the parent compound of the series. For higher homologues, other and more cumbrous methods must be used. This results in the position that whilst keten and its dimer can, and are, prepared industrially in considerable quantity, the remaining homologues are, at present, laboratory curiosities.

Staudinger, who conducted most of the early research on substituted ketens, divided them into two classes : aldoketens in which at least one free hydrogen atom was attached to the keten group as in $R\,.\,CH{=}CO$, and ketoketens in which the keten group is fully substituted as in $R_2C{=}CO$. The alternative method of regarding the two classes as mono- and di-substituted derivatives of keten is the basis of the usually accepted nomenclature. According to the provisions of the Liège Convention, the existing nomenclature for ketens is preserved, substituted ketens being regarded as derivatives of $CH_2{=}CO$, e.g.,

Keten	$CH_2{=}CO$
Methyl ethyl keten	$CH_3(C_2H_5)C{=}CO$
Phenyl keten	$C_6H_5\,.\,CH{=}CO$

Although the ketens are extremely reactive substances, not many have been prepared. The chief members of the family, with their physical properties, are listed in Table I. It may be remarked here that, in general, the monosubstituted ketens are colourless ; the disubstituted ketens are orange or yellow.

KETEN, CH_2CO

Although keten can be obtained in small quantity by the action of a zinc-copper couple on an ethereal solution of bromoacetyl bromide,

$$Br\,.\,CH_2\,.\,CO\,.\,Br + Zn \longrightarrow CH_2{=}CO + ZnBr_2,$$

by the action of trimethylamine [3] on acetyl bromide :—

$$N(CH_3)_3 + CH_3\,.\,CO\,.\,Br \longrightarrow CH_2{=}CO + [NH(CH_3)_3]Br,$$

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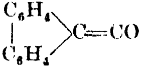
[1] Staudinger, *Ber.*, 1905, **38**, 1735.

[2] Wilsmore and Stewart, *Nature*, 1907, **76**, 510 ; Wilsmore, *J.C.S.*, 1907, **91**, 1938.

[3] Jones and Whalen, *J.A.C.S.*, 1925, **47**, 1343.

TABLE 1

Name	Formula	B.P.	M.P.	Colour
Keten	$CH_2{=}CO$	$-41°$	$-134{\cdot}6°$	Colourless
Methyl keten	$CH_3CH{=}CO$	—		
Ethyl keten	$C_2H_5CH{=}CO$	—		
Phenyl keten	$C_6H_5CH{=}CO$	—		
Dimethyl keten	$(CH_3)_2C{=}CO$	34°	$-98°$	Pale yellow
Methyl ethyl keten	$CH_3(C_2H_5)C{=}CO$	$-27°$/12 mm.	—	Yellow
Diethyl keten	$(C_2H_5)_2C{=}CO$	89°	—	Citron
Dipropyl keten	$(C_3H_7)_2C{=}CO$	30°/11 mm.	—	Yellow
Diallyl keten	$(C_3H_5)_2C{=}CO$	30°/9 mm.	$-123°$	Colourless
Methyl phenyl keten	$CH_3(C_6H_5)C{=}CO$	74°/12 mm.	—	Orange
Methyl benzyl keten	$CH_3(C_6H_5 . CH_2)C{=}CO$	46°/0·1 mm.	—	Yellow
Diphenyl keten	$(C_6H_5)_2C{=}CO$	146°/12 mm.	—	Orange
Dibenzyl keten	$(C_6H_5 . CH_2)_2C{=}CO$	121°/12 mm.	—	Pale yellow
Diphenylene keten	 $\begin{matrix} C_6H_4 \\ \vert \\ C_6H_4 \end{matrix}\!\!>\!C{=}CO$	—	90°	Scarlet

and by the pyrolysis of acetylene containing small quantities of oxygen,[1] it is more conveniently made by the pyrolysis of acetone, which takes place readily at a temperature of 600-700°. The reaction,

$$CH_3COCH_3 \longrightarrow CH_2{=}CO + CH_4$$

has been the subject of much study, especially in regard to the effect of physical conditions on the yield of keten. A 'ceiling' is set to the temperature which can safely be used for the pyrolysis of acetone by the fact that the decomposition of keten itself commences to be appreciable at 600°. Schmidlin and Bergmann [2] report that the reaction takes the course

$$2CH_2{=}CO \longrightarrow 2CO + CH_2{=}CH_2$$

but this represents only the main course of the decomposition. Hale [3] has reported the simultaneous formation of small quantities of naphthalene in this reaction. Rice and Walters [4] have put forward a chain mechanism to account for the formation of keten :—

$$\begin{aligned} CH_3 . CO . CH_3 &\longrightarrow 2CH_3{—} + CO \\ CH_3 . CO . CH_3 + CH_3{—} &\longrightarrow CH_4 + CH_3 . CO . CH_2{—} \\ CH_3 . CO . CH_2{—} &\longrightarrow CH_3 + CH_2{=}CO \\ CH_3{—} + CH_3 . CO . CH_2{—} &\longrightarrow CH_3 . CO . CH_2CH_3 \end{aligned}$$

The presence of methyl ethyl ketone in the recovered liquid from the pyrolysis of pure acetone has been demonstrated.

Muskat was able to show that methylene, obtained by heating iodomethylmagnesium iodide in dry nitrogen, combined with carbon monoxide to give keten :—

$$ICH_2 . MgI \longrightarrow MgI_2 + CH_2 \xrightarrow{+CO} CH_2{=}CO$$

Keten, a colourless gas at ordinary temperatures, has a pronounced and unpleasant odour ; it is unstable and tends to polymerise to diketen (often called 'acetylketen'), $CH_3CO . CH{=}CO$. This polymerisation takes place rapidly at ordinary temperatures, and if conditions are suitably controlled, a substantial yield of diketen is obtained. Under uncontrolled conditions some dehydracetic acid is formed (see p. 471).

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[1] Ingold, *J.C.S.*, 1924, **125**, 1528.

[2] Schmidlin and Bergmann, *Ber.*, 1910, **43**, 2821.

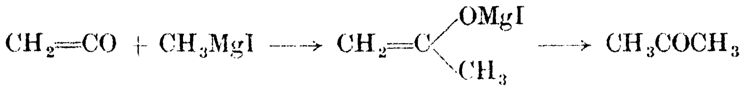
[3] Hale, *Nature*, 1937, **140**, 1017.

[4] Rice and Walters, *J.A.C.S.*, 1941, **63**, 1701.

The chemical properties of keten may be divided into two groups, those involving the ketonic group and those involving the ethylenic bond ; the latter predominate. It may be pointed out that keten is the stable form of the simplest acetylenic alcohol :—

$$CH{\equiv}C\,.\,OH \longrightarrow CH_2{=}CO$$

Amongst the few reactions that involve the carbonyl group, the action of Grignard reagents is of interest :—[1]



It will be seen that the original ketone, acetone, is regenerated.

Halogens attack the ethylenic bond of keten, giving almost instantaneous addition in the case of chlorine and bromine, the products being chloroacetyl chloride and bromoacetylbromide respectively :—

$$CH_2{=}CO + Cl_2 \longrightarrow CH_2Cl\,.\,COCl$$

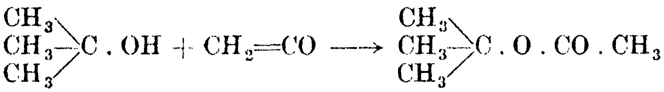
Acetyl chloride or bromide is obtained from liquid hydrogen chloride or bromide [2]

$$CH_2{=}CO + HBr \longrightarrow CH_3\,.\,COBr$$

Considerable interest centres round the addition of keten to hydroxylic compounds, all of which appear to react by addition to the ethylenic bond, thus

(1) Water yields acetic acid, $CH_2{=}CO + H_2O \longrightarrow CH_3\,.\,COOH$

(2) Alcohols yield acetic esters, $CH_2{=}CO + C_2H_5OH \longrightarrow CH_3\,.\,COOC_2H_5$. This reaction has been extended to afford a manufacturing process for obtaining the pure tertiary and secondary acetates. *ter*-Butyl alcohol, for example, gives a 90 per cent., or better, yield of *ter*-butyl acetate when acetylated with keten. A trace of concentrated sulphuric or *p*-toluene sulphonic acid is necessary with tertiary alcohols.[3]



Bornyl acetate and linalyl acetate are also prepared industrially in this manner.

(3) Hydrogen peroxide yields peracetic acid, and if the reaction be continued, acetyl peroxide :—[4]

$$CH_2{=}CO + H_2O_2 \longrightarrow CH_3\,.\,COO\,.\,OH \xrightarrow{CH_2=CO} [CH_3\,.\,CO\,.\,O]_2$$

(4) Phenols yield the acetyl derivatives.

(5) Acids yield acid anhydrides ; thus, acetic acid is readily converted to its anhydride by this method :—

$$CH_2{=}CO + CH_3\,.\,COOH \longrightarrow (CH_3\,.\,CO)_2O$$

a procedure used industrially to regenerate " weak " acetic anhydride for artificial silk manufacture. Other acids give mixed anhydrides, e.g.,

$$CH_2{=}CO + C_3H_7\,.\,COOH \longrightarrow CH_3\,.\,CO\,.\,O\,.\,CO\,.\,C_3H_7$$

but these mixed anhydrides are of little interest, decomposing to the homogeneous structures on distillation, thus :—

$$2CH_3\,.\,CO\,.\,O\,.\,CO\,.\,C_3H_7 \longrightarrow (CH_3\,.\,CO)_2O + (C_3H_7\,.\,CO)_2O$$

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[1] Deakin and Wilsmore, *J.C.S.*, 1910, **97**, 1968.

[2] Wilsmore and Chick, *Proc. Chem. Soc.*, 1908, **24**, 77.

[3] Hurd and Roe, *J.A.C.S.*, 1934, **56**, 2216 ; 1936, **58**, 962 ; 1939, **61**, 3355.

[4] Ans and Frey, *Ber.*, 1912, **45**, 1845.

(6) Keten reacts with the amino group of hydroxylamine in preference to the hydroxyl, yielding a hydroxamic acid :—

$$CH_2{=}CO + NH_2OH \longrightarrow CH_3 . CO . NH . OH$$

this, however, is acetylated normally through the hydroxyl group when the action of keten is continued, whilst finally, by the action of a third

$$\begin{aligned} CH_3 . CO . NH . OH + CH_2CO &\longrightarrow CH_3 . CO . NH . O . CO . CH_3 \\ &\longrightarrow (CH_3 . CO)_2N . O . CO . CH_3 \end{aligned}$$

molecule of keten, a trihydroxamic acid can be obtained.[1]

Keten is a particularly valuable reagent for acetylation of primary amino groups. Aniline, in an inert solvent, is quantitatively converted to acetanilide by the passage of keten :—

$$C_6H_5 . NH_2 + CH_2{=}CO \longrightarrow C_6H_5 . NH . CO . CH_3$$

and the reaction may be extended to numerous other amines. Thus, phenacetin (acetyl-*p*-phenetidine) can be obtained from phenetidine. Most secondary amines react similarly, and even diphenylamine may be made to yield its acetyl derivative in 30-40 per cent. yield. In general,[2] keten reacts so much more readily with amino compounds than with water, that aqueous solutions of amines can be acetylated in good yield,[2] and in this way excellent yields of acetylamino-acids can be obtained from aqueous solutions or suspensions of the amino-acids.

With hydrazines, keten reacts to give acyl derivatives :—

$$C_6H_5 . NH . NH_2 + CH_2{=}CO \longrightarrow C_6H_5 . NH . NH . CO . CH_3$$

The action of keten[3] on hydrazoic acid is to give a transitory azide which readily loses nitrogen forming the corresponding isocyanate :—

$$CH_2{=}CO + HN_3 \longrightarrow CH_3 . CO . N_3 \longrightarrow CH_3 . NCO + N_2$$

Keten can take part in the Friedel-Crafts reaction,[4] giving an aryl ketone, e.g.,

$$C_6H_6 + CH_2{=}CO \xrightarrow{AlCl_3} C_6H_5 . COCH_3,$$

but the yield seldom exceeds 30 per cent. of the theoretical quantity.

Air is almost without action on ketene, although the substituted ketens show strong autoxidation.

Diketen

Diketen, acetyl-keten ($CH_3CO . CH{=}CO$), is formed readily by the controlled polymerisation of keten. It is a liquid, solidifying to a crystalline mass, m. − 7·5°, b. 127°. It has a penetrating odour, and is unstable at ordinary temperatures, turning slowly to a series of products of higher molecular weight of which dehydracetic acid is the preponderating constituent.

The reactivity of diketen is phenomenal ; with alcohols it gives esters of acetoacetic acid :—

$$CH_3CO . CH{=}CO + C_2H_5OH \longrightarrow CH_3COCH_2COOC_2H_5.$$

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[1] Hurd and Cochran, *J.A.C.S.*, 1923, **45**, 515.

[2] Oliveri-Mandala and Caldevaro, *Gazz. Chim. Ital.*, 1913, **43**, 538.

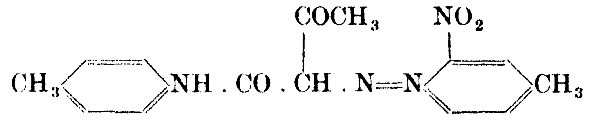
[3] Williams and Osborn, *J.A.C.S.*, 1939, **61**, 3438.

[4] Bergmann and Stern, *Ber.*, 1930, **63***B*, 437.

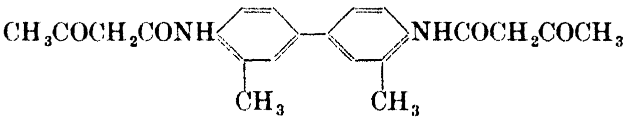
With amines it gives anilides :—

$$C_6H_5NH_2 + CH_3 . CO . CH{=}CO \longrightarrow C_6H_5 . NH . CO . CH_2 . COCH_3$$

which are valuable intermediates in the production of Hansa yellows, e.g.,

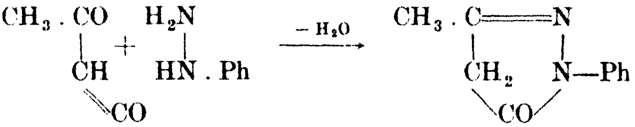


The condensation goes quite readily even when the amine is a complex substance, e.g., *o*-tolidine, which is readily converted by diketene to its *bis*-acetoacetyl derivative :—



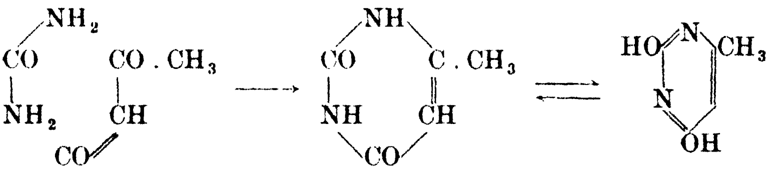
from which valuable dye-pigments are obtainable.

With phenylhydrazine, 1-phenyl-3-methyl-5-pyrazolone, an intermediate in the manufacture of antipyrine is obtained :—

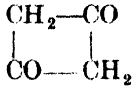


This substance yields antipyrine on methylation.

Diketen reacts with urea to give methyl uracil, and the reaction may be extended to substituted ureas.



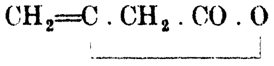
The structure of diketen has been the subject of much discussion and experiment. At one time it was thought to be a *cyclo*-butane derivative (1),



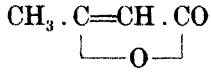
(1)

$CH_3 . CO . CH{=}CO$

(2)



(3)



(4)

but the conception was dropped about 1917 when various *cyclo*-butane derivatives were prepared and shown to be entirely dissimilar in properties to the dimeric ketens. Boese [1] suggested a vinylaceto-β-lactone structure (3). This, however, does not fit in with the parachor or the ozonolysis to pyruvic acid [2] and the accepted structural conception is that of an equilibrium mixture of acetylketen (2) and croton-β-lactone (4).

SUBSTITUTED KETENS

The simple monosubstituted analogues of keten—methyl, ethyl and phenyl keten—are so unstable as to be virtually unobtainable in the pure state. They may be obtained in ethereal solution in low yield by allowing bright zinc turnings to react upon the ethereal solution of the appropriate bromacyl bromide, e.g.,[1]

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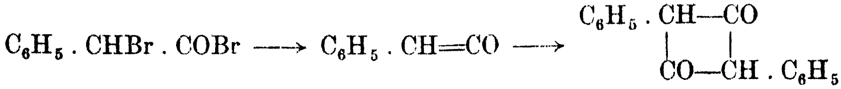
[1] Boese, *J. Ind. Eng. Chem.*, 1940, **32**, 16.

[2] Hurd *et al.*, *J.A.C.S.*, 1940, **62**, 1147 ; 1941, **63**, 2174.



$$C_6H_5\,.\,CHBr\,.\,COBr \longrightarrow C_6H_5\,.\,CH{=}CO \longrightarrow \begin{array}{l} C_6H_5\,.\,CH{-}CO \\ \quad\;\, | \qquad\;\; | \\ \quad CO{-}CH\,.\,C_6H_5 \end{array}$$

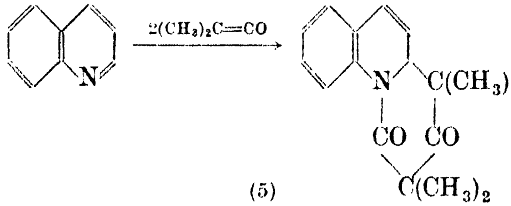
These ketens are stated readily to polymerise, giving *cyclo*butane derivatives which are comparatively inert chemically.

The dialkyl and diaryl ketenes are more readily obtainable. Thus, dimethyl keten is a liquid boiling at 34°, and can be isolated by any of the following processes :—

(1) The debromination with zinc of α-bromo*iso*butyryl bromide.
(2) The thermal decomposition of the mixed anhydride of dimethyl malonic and phenylacetic acids.
(3) The thermal decomposition of dimethyl malonic anhydride.[2]

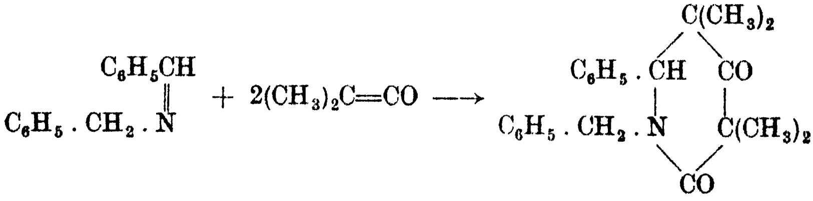
The last is by far the best practical method of obtaining dimethyl keten ; dimethyl malonic acid is dissolved in ice-cold acetic anhydride and subjected to very slow distillation under reduced pressure (40-50 hours). The temperature finally rises to about 100°, and the residue of crude dimethyl malonic anhydride gives, on heating, about 90 per cent. of the theoretical quantity of dimethyl keten. Dimethyl keten is characterised by certain properties which are quite distinct from those of keten itself. In particular is this difference shown in the colour which is yellow both in liquid and vapour form, and in the autoxidation to form an explosive, highly insoluble peroxide.[3] In operations using dimethyl keten the greatest care must be taken to exclude all traces of air to avoid the formation of this dangerously susceptible substance which explodes on touching, or even spontaneously.

Dimethyl keten polymerises rapidly, being entirely converted in a few hours at ordinary temperature into a mixture of dimer (liquid, b. 170-171°, of pleasant peppermint odour), and tetramer (solid).[4] Most interesting products are obtained by the action of dimethyl keten on quinoline and its derivatives (5),



(5)

the reaction affording a method of synthesising phenanthridines with angular nitrogen. Dimethyl keten adds also to the double bond of such substances as benzylidene benzylamine, yielding piperidine compounds :—



$$\begin{array}{r} C_6H_5CH \\ \| \\ C_6H_5\,.\,CH_2\,.\,N \end{array} + 2(CH_3)_2C{=}CO \longrightarrow \begin{array}{c} \qquad\qquad C(CH_3)_2 \\ C_6H_5\,.\,CH \qquad CO \\ | \qquad\qquad | \\ C_6H_5\,.\,CH_2\,.\,N \qquad C(CH_3)_2 \\ \qquad\qquad CO \end{array}$$

Dimethyl keten also reacts readily with carbon dioxide yielding a series of crystalline solids which have the composition $R_2\,.\,CO_2$, $R_3\,.\,2CO_2$; $R_4\,.\,3CO_2$

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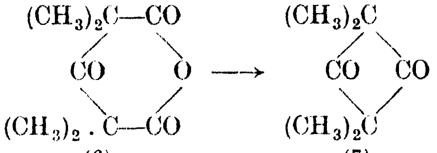
[1] Staudinger, *et al.*, *Ber.*, 1908, **41**, 906 ; 1911, **44**, 533.
[2] Staudinger *ibid.*, 1908, **41**, 2208 ; *Helv. Chim. Acta*, 1925, **8**, 306.
[3] Staudinger *et al. loc. cit.*
[4] Staudinger and Klever, *Ber.*, 1907, **40**, 1149.

(where R = dimethyl keten). The simplest of these appears to be[1] tetramethylacetone dicarboxylic acid anhydride (6), and on boiling with concentrated hydrochloric acid yields tetramethyl *cyclo*butane dione (7).

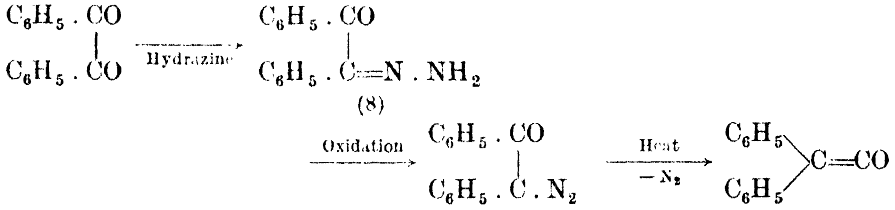


(6) (7)

The availability of the diazoketones from acid chlorides and diazomethane[2] has led to new methods for the preparation of ketens, by the sequence[3] of reactions.

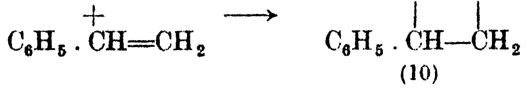
$$R.COCl + CH_2N_2 \xrightarrow{-HCl} R.CO.CHN_2 \xrightarrow{-N_2} R.CH{=}CO$$

Of the other ketens which have from time to time been prepared, diphenyl keten is the best known and most important. It is more easily prepared from the hydrazone of benzil than by the original method of Staudinger.



(8) (9)

Benzil is converted by hydrazine to the monohydrazone (8); this, on oxidation with yellow mercuric oxide gives the substance 'azibenzil' (9), which is unstable and gives off nitrogen spontaneously; on gentle warming in benzene solution[4] the evolution of nitrogen is completed, and on removal of the benzene and vacuum distillation of the residue, diphenyl keten is obtained as a yellow-orange liquid; attempted distillation at ordinary pressures leads to decomposition to carbon monoxide and fluorene. Owing to its ease of preparation and slow polymerisation, considerable experimental work has been carried out with diphenyl keten, the reactions of which are better known than those of keten itself. When heated with quinoline for some hours, two polymers are formed, one m. 176° and a second m. 245°; the latter is the symmetrical tetraphenyl *cyclo*butanedione. The reactions of diphenyl keten with water, alcohols, phenols and amines follows out the course to be expected from the corresponding reactions with keten itself. Diphenyl keten also shows a strong tendency to add to ethylenic double bonds. Thus, the reaction with styrene gives a triphenyl *cyclo*butanone (10). With ketones the primary



(10)

reaction product breaks down, giving carbon dioxide and a tetrasubstituted ethylene; thus, diphenyl keten and methyl ethyl ketone give 2-methyl 2-ethyl

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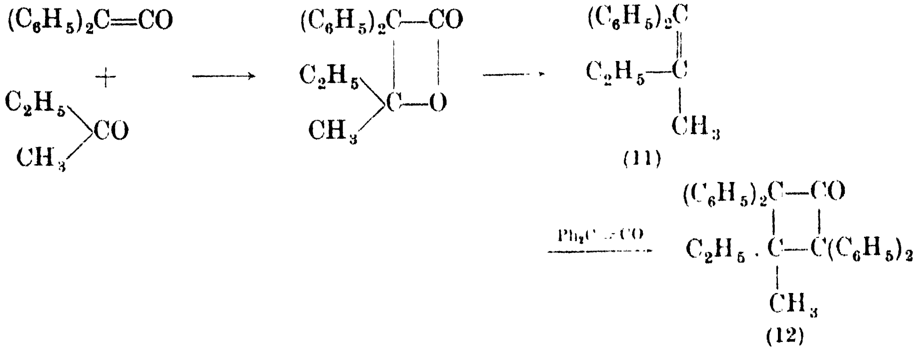
[1] Staudinger, Felix and Harder, *Helv. Chim. Acta*, 1925, **8**, 306.

[2] Arndt *et al.*, *Ber.*, 1927, **60**, 1364; 1928, **61**, 1122, 1949; Robinson and Bradley, *J.C.S.*, 1938, 2904.

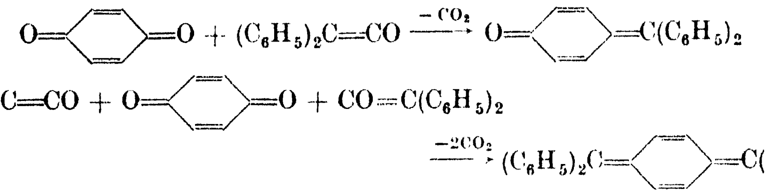
[3] Schroeter, *Ber.*, 1909, **42**, 2346; 1916, **49**, 2704.

[4] Ploeg, *Rec. Trav. Chim.*, 1926, **45**, 342.

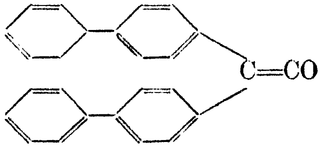
1, 1-diphenyl-ethylene (11). Further reaction of diphenyl keten leads to the hexa-substituted *cyclo*butanone (12)



Quinones lead to interesting hydrocarbons, the derivatives of which show spiro-asymmetry.



Shilov and Burmistrov have prepared di-*p*-xenylketen in order to ascertain the effect of large groups on the reactivity of the keten group :—



They obtained it as a yellow solid, m. 197°, which gives the normal reactions of a keten.

KETEN ACETALS

In the course of extensive researches on the synthesis of ketonic esters Scheibler and Ziegner[1] claimed to have obtained keten acetal—a substance which would account for the low yields in many β-ketonic ester syntheses (*vide* acetoacetic ester). These investigators demonstrated that when sodium reacts upon ethyl acetate in ethereal solution, the alkali salt of the enol form $CH_2=C(OEt)OK$ is formed. This can react with, say, ethyl benzoate to give benzoylacetic ester in the normal way ; on the other hand, Scheibler and Ziegner claimed that a considerable portion reacts thus :—

$$CH_2=C(OEt)ONa + C_6H_5 . COOEt \longrightarrow C_6H_5 . COONa + CH_2=C(OEt)_2$$

The existence of this compound has been denied,[2] but the work of McElvain has proved conclusively that the acetal exists, although its action and presence in the β-ketonic ester synthesis has not been satisfactorily demonstrated. Keten acetal[3] is readily prepared in good yield by allowing α-bromo ethyl

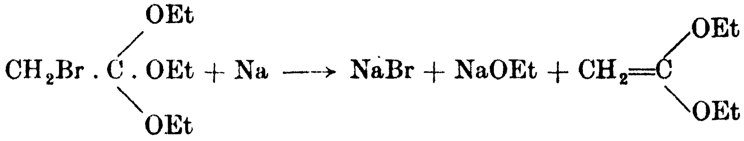
---

[1] Scheibler and Ziegner, *Ber.*, 1922, **55***B*, 789.

[2] Adickes and Meister, *ibid.*, 1935, **68***B*, 2191.

[3] Walters and McElvain, *J.A.C.S.*, 1940, **62**, 6223.

ortho-acetate (13) to drop slowly into a gently boiling suspension of sodium in benzene :—



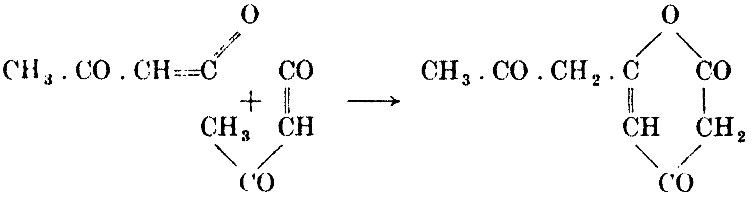
$$CH_2Br\,.\,C(OEt)_3 + Na \longrightarrow NaBr + NaOEt + CH_2{=}C(OEt)_2$$

(13)

DEHYDRACETIC ACID

Geuther [1], in 1863, commenced a series of researches on the formation of acetoacetic ester, and observed that during its distillation a quantity of crystalline material was obtained to which he gave the name dehydracetic acid. Conrad obtained it later [2] by heating acetoacetic ester under pressure, and Oppenheim and Precht [3] by the pyrolysis of acetoacetic ester. It is also observed during the formation of diketen from monoketen and by suitable catalytic means may be obtained in almost theoretical yield from diketen. Its empirical formula shows it to be a tetramer of keten—$C_8H_8O_4$. It is a white crystalline substance, m. 109°, of which one part is soluble in 100 parts of water at ordinary temperatures.

Dehydracetic acid is only a feeble acid and conductometric experiments indicate the absence of a carboxyl group, thus automatically eliminating some of the earlier formulæ. In view of its almost quantitative formation from diketen under suitable conditions, the two formulæ (14) and (15), suggested by Collie and Feist respectively, most nearly express the genesis and properties of dehydracetic acid :—



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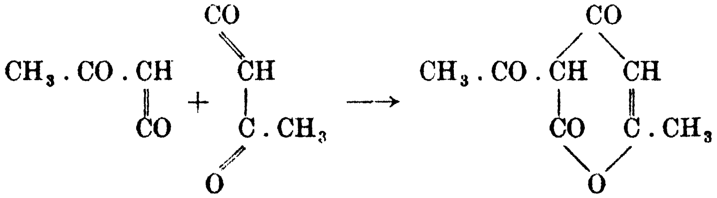

(15)

It is almost impossible to adduce evidence which will clearly differentiate between these two structures ; the weight of evidence appears to be slightly in favour of Feist's formula.

CARBON SUBOXIDE

Diels and Wolf,[4] in 1906, discovered this third oxide of carbon, C_3O_2, among the products of dehydration of malonic ester, using phosphorus pentoxide.

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[1] Geuther, *Z. f. Chemie*, 1866 (2), **2**, 8.

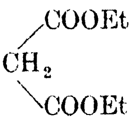
[2] Conrad, *Ber.*, 1874, **7**, 688.

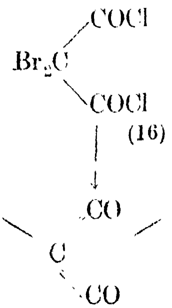
[3] Oppenheim and Precht, *ibid.*, 1876, **9**, 323, 1099.

[4] Diels and Wolf, *ibid.*, 1906, **39**, 689.

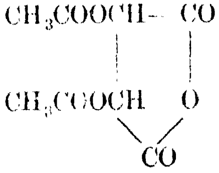
The structure, OC=C=CO, shows it as a diketen (in French technical literature it is referred to as " Propane diketen ").

The Diels method of preparation referred to above gives only a few per cent. yield; the best yields are obtained from dibromomalonyl dichloride (16) when treated with bright zinc turnings, in the presence of ether.[1] Another practical method is to heat diacetyl tartaric anhydride (17) when carbon suboxide is formed :—





(16)



(17)

Carbon suboxide is a colourless gas with an unpleasant odour. It condenses readily and has b.p. 7°. Its reactions are very reminiscent of those of keten itself; it reacts with ammonia, water, alcohols and amines quite normally; it also gives pyrazolones with hydrazine derivatives. It resembles mono-keten in chemical behaviour in that it does not react with quinone or benzylidene aniline.

APPENDIX I

LITERATURE REFERENCES

Ketens

A. B. **Boese**. *Ind. Eng. Chem.*, 1940, 32, **32.** Contains an account of diketen and its uses; a useful bibliography (about 50 papers) is attached.

C. K. **Ingold**. *Ann. Rep. Chem. Soc.*, 1925, **22,** 118 (Keten-monoxides).

H. **Staudinger**. "Die Keten", 1912, Stuttgart. (Also bound in 'Chemie in Einzeldarstellungen'). Contains only the first few years of development of the chemistry of ketens. Historical value only.

Carbon Suboxide

E. C. C. **Baly**. *Ann. Rep. Chem. Soc.*, 1917, **14,** 48.

H. J. H. **Fenton**. *Ann. Rep. Chem. Soc.*, 1906, **3,** 101.

L. H. **Ryerson**, and K. **Kobe**. *Chem. Rev.*, 1930, **7,** 479

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[1] Staudinger and Bereza, *Ber.*, 1908, **41,** 4461.

CHAPTER VIII

ACIDS AND ESTERS

> "Also guaiacum and divers other woods, that do not at all taste sour, will, being distilled in retorts, afford spirits, that are furnished with store of acid particles, which as I have tried will hiss upon alkalies, and will dissolve coral, and even lead itself calcined to minium and make *saccharum saturni* of it."
>
> — R. BOYLE.

A wide variety of organic compounds show acid properties, and might be classed as acids if salt-formation and the neutralisation of alkalies were the sole criteria.[1] Thus, uric acid and phenol (carbolic acid) both give salts with alkalies and yield enough hydrogen ion in solution to give acid indicator reactions. Again, reference has been made to the behaviour of the hydrogen of the methylene group in *cyclo*pentadiene and its analogues where 'salt' formation with metals is possible. It will be seen that any organic compound containing hydrogen may be written [R]H, and that the justification of the square brackets, indicating an electrovalency, depends on the criteria agreed upon for detecting this condition. No such justification can be found in the case of CH_4, but under certain conditions $CHCl_3$ may be written $[CCl_3]H$ and CH_3NO_2 as $[CH_2NO_2]H$. It will, therefore, be realised that 'acidity' is a somewhat vague concept, and that if expressed in terms of the symbols

$$RH \rightleftharpoons [R]H \rightleftharpoons [R]' + H^{\cdot}$$

it comprises a range of substances with all shades of variation in the balance of equilibrium, depending largely on the effect of adjacent groups on the lability of the hydrogen.

The formation which most consistently displays all the phenomena of acidity is the —CO . OH (carboxyl) group which can always be written —COO]H with justification, and it is to substances displaying this characteristic group, that this chapter is confined.

FORMATION OF THE CARBOXYL GROUP

Before considering individual groups of acids it is advisable to discuss methods of producing acids; they may be divided into two main groups: (*a*) the introduction of the carboxyl group; or (*b*) the manipulation of the structure of substances in which the corresponding carbon atoms are already present. The latter process may be carried out by the following methods:—

(1) *Direct Oxidation.*—This is applicable to both aliphatic and aromatic hydrocarbons, although the latter are more usually associated with the process. If the higher aliphatic hydrocarbons are treated with air or oxygen, in the presence of a catalyst, the terminal methyl group is converted to carboxyl

$$CH_3(CH_2)_nCH_3 \longrightarrow CH_3(CH_2)_nCOOH.$$

This process is used industrially for producing mixtures of fatty acids from hydrocarbons, but is seldom applied to the production of individual acids. On the other hand, the oxidation of aromatic hydrocarbons is one of the most successful methods for obtaining aromatic acids. The side-chains of aralkyl hydrocarbons are oxidised to carboxyl, toluene giving benzoic acid whilst *p*-xylene and mesitylene give terephthalic and trimesic acids respectively :—

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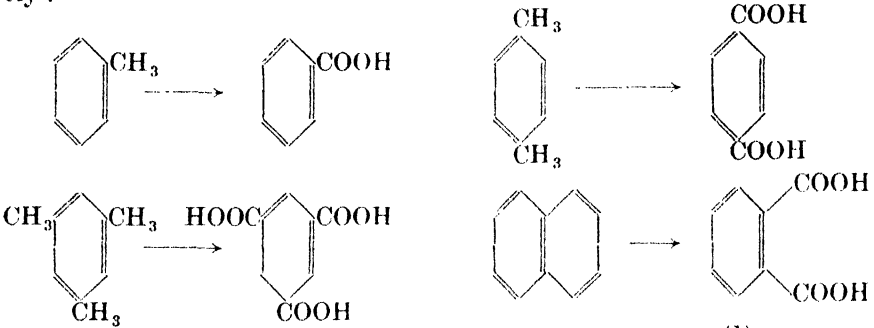
[1] Bell, The use of the terms "acid" and "base", *Quarterly Reviews of Chem. Soc.*, 1947, **1**, 113.



(1)

Further, *o*-dicarboxylic acids can be obtained by oxidising fused ring hydrocarbons, such as naphthalene, which gives phthalic acid (1) or its anhydride. Chromic or permanganate reagents are frequently used for these oxidations, although many of them can be performed directly with air or oxygen in the presence of a controlling catalyst.

(2) *From a Halogenated Hydrocarbon.*—Many routes from the alkyl or aryl bromide to the acid exist, some of which are indicated in Table I. It will be observed that the shortest route is via the Grignard compound :—

$$\mathrm{EtBr} \longrightarrow \mathrm{EtMgBr} \longrightarrow \mathrm{EtCOOMgBr} \longrightarrow \mathrm{EtCOOH}$$

which with carbon dioxide yields an addition compound readily decomposed by dilute mineral acids to the required organic acid and a magnesium salt.

A variation of this process is the action of ethyl carbonate on the Grignard compound at low temperatures and under conditions which minimise attack of the ester formed, by excess of Grignard compound :—

$$\mathrm{EtBr} \longrightarrow \mathrm{EtMgBr} + \mathrm{CO(OEt)_2} \longrightarrow \mathrm{EtCOOEt} + \mathrm{EtOMgBr}.$$

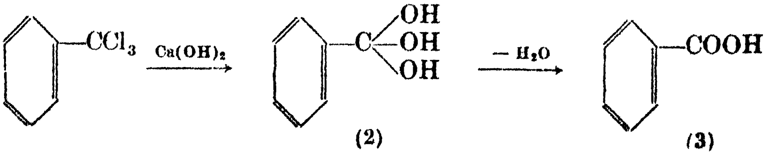
In this case the ester is produced, but may be hydrolysed easily to the acid.

The halogen compound may be converted to the corresponding alcohol, and the latter oxidised to the acid either directly or with isolation of the aldehyde. In this way it will be seen that the alcohol or aldehyde (usually more easily available than the halogen compound)

$$\mathrm{EtBr} \longrightarrow \mathrm{EtOH} \longrightarrow \mathrm{CH_3\,.\,CHO} \longrightarrow \mathrm{CH_3COOH}$$

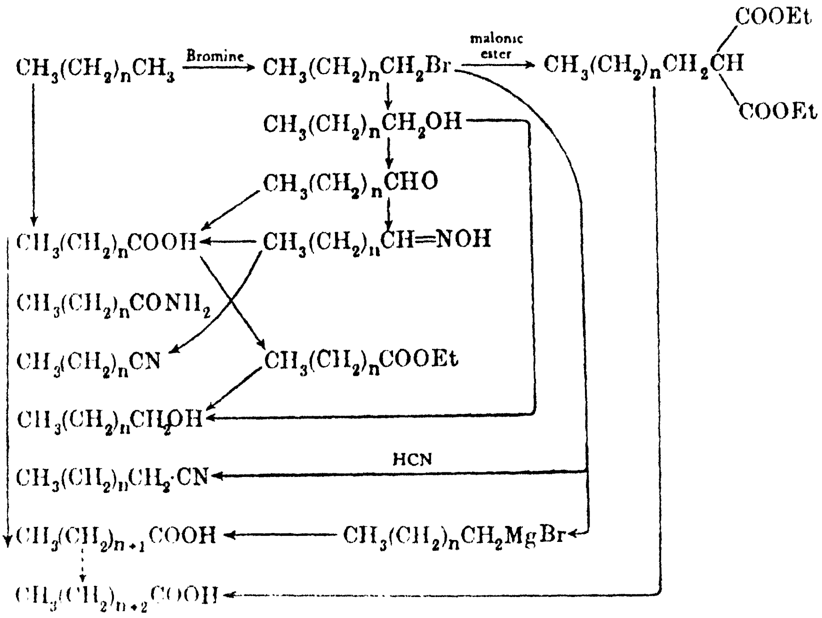
may itself be used as a source of the corresponding acids. Further, it will be noted that when one of the latter processes is used, the final acid has the same number of carbon atoms as the original halogen compound ; when a Grignard method is used the acid has one more carbon atom than the original halide. Acids with two more carbon atoms than the original halogen compound can be obtained by condensing the latter with sodio-malonic ester and decomposing the resultant substituted malonic ester by hydrolysis ; the course of the reaction is indicated in Table I. In addition, alternative methods of proceeding up the acid series are known, and these also are indicated in Table I.

In the aromatic series the direct decomposition of polyhalogenated compounds is of importance ; thus, the first reaction of alkalies on substances such as benzotrichloride is to form an ortho acid (2) which spontaneously dehydrates to the carboxyl form (3).

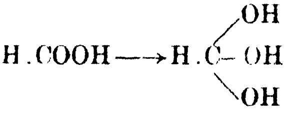


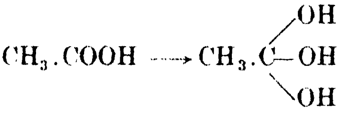
(2) (3)

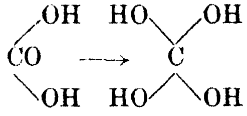
TABLE I

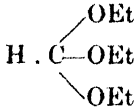


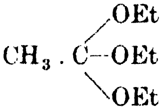
It may be added that the conception of ortho acids is widely used in aliphatic chemistry to represent the fully hydrated forms of carboxylic derivatives ; thus the three acids, formic, carbonic and acetic are potentially able to form *ortho*formic, *ortho*carbonic and *ortho*acetic acids, thus :—

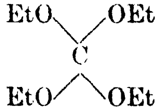

*ortho*formic acid


*ortho*acetic acid


*ortho*carbonic acid


*ortho*formic ester


*ortho*acetic ester


*ortho*carbonic ester

The free acids do not exist, but their esters are well-known and are important raw materials for syntheses.

(3) *The Oxidation of Aldehydes.*—This method has been known and used for the preparation of acids for a long period, and it was by its use that Laurent[1] discovered œnanthic acid in 1837 ; at present there are only a few instances where the aldehyde is so plentiful that it can be used as a source of the acid. The usual oxidising agents are permanganates, or chromates in the presence of acids, and hydrogen peroxide in the presence of manganese salts. The reaction between water vapour and an aldehyde to give hydrogen and the corresponding acid takes place readily at 350° in the presence of a copper chromite catalyst

$$R.CHO + H_2O \longrightarrow R.COOH + H_2.$$

---

[1] Laurent, *Ann. Chim. Phys.*, 1837, **66**, 164.

Mention should also be made of Cannizzaro's reaction in which an aromatic aldehyde in the presence of potassium hydroxide gives a mixture of the corresponding alcohol and the potassium salt of the acid :—

$$2RCHO \longrightarrow R\,.\,COOH + RCH_2OH.$$

The reaction can be extended to the aliphatic aldehydes[1] and Shipley[2] in investigating the reaction showed that formaldehyde gave a similar reaction, but that two stages could be recognised

$$HCHO + KOH \longrightarrow H_2 + H\,.\,COOK$$
$$HCHO + H_2 \longrightarrow CH_3OH$$

some of the hydrogen escapes and may be collected as such. If some substance is present which is a less reluctant hydrogen-acceptor than formaldehyde, e.g., benzaldehyde, it is reduced. Yields up to 90 per cent. of benzyl alcohol are obtained from benzaldehyde and formaldehyde in the presence of sodium hydroxide :—

$$C_6H_5\,.\,CHO + HCHO + NaOH \longrightarrow C_6H_5CH_2OH + H\,.\,COONa.$$

An important variant of this reaction is the interaction of two molecules of aromatic aldehyde in the presence of aluminium ethoxide (or butyloxide) to give the ester.[3] In this way, benzyl benzoate, the specific treatment for scabies infestation, is obtained industrially.

$$2C_6H_5CHO \longrightarrow C_6H_5CH_2OCOC_6H_5.$$

(4) *Oxidation of Alcohols.*—Primary alcohols are oxidised readily by most of the common reagents to the corresponding acids. The reaction can be brought about readily by catalysis. If acid oxidising agents are used, the reaction mixture is often made strongly alkaline and boiled, at the end of the reaction, to hydrolyse any ester formed during the oxidation.

(5) *From Carbon Monoxide.*—Carbon monoxide reacts readily with potassium hydroxide forming potassium formate :—

$$KOH + CO \longrightarrow H\,.\,COOK,$$

a reaction which has been utilised for the industrial production of formic acid and its salts. Gautier and Frolich[4] extended this method of preparation to the sodium salts of acetic and propionic acid by treating sodium methoxide and ethoxide with carbon monoxide at 160° :—

$$C_2H_5ONa + CO \longrightarrow C_2H_5COONa.$$

The yield falls off rapidly as the series is ascended. It is probably this reaction which accounts for the presence of about ½ per cent. of acetic acid in the Fischer-Tropsch synthesis of methanol, excess of carbon monoxide reacting at the catalyst surface with methanol :—

$$2H_2 + CO \longrightarrow CH_3\,.\,OH + CO \longrightarrow CH_3COOH.$$

The use of ketonic or malonic ester synthesis in the preparation of acids is discussed in Appendix II to this chapter.

(6) *Methods involving the Saponification of Nitriles or Amides.*—Any alkyl or aryl cyanide may be saponified by boiling with alkalies or acids to give the corresponding carboxylic acid and ammonia. In some cases the acid amide stage can be distinguished, although frequently the acid amide is more sensitive to hydrolytic reagents than is the nitrile, so that it is destroyed as fast as formed.

---

[1] Palfray and Sabotay, *Bull. Soc. Chim.*, 1934, **1**, 903.

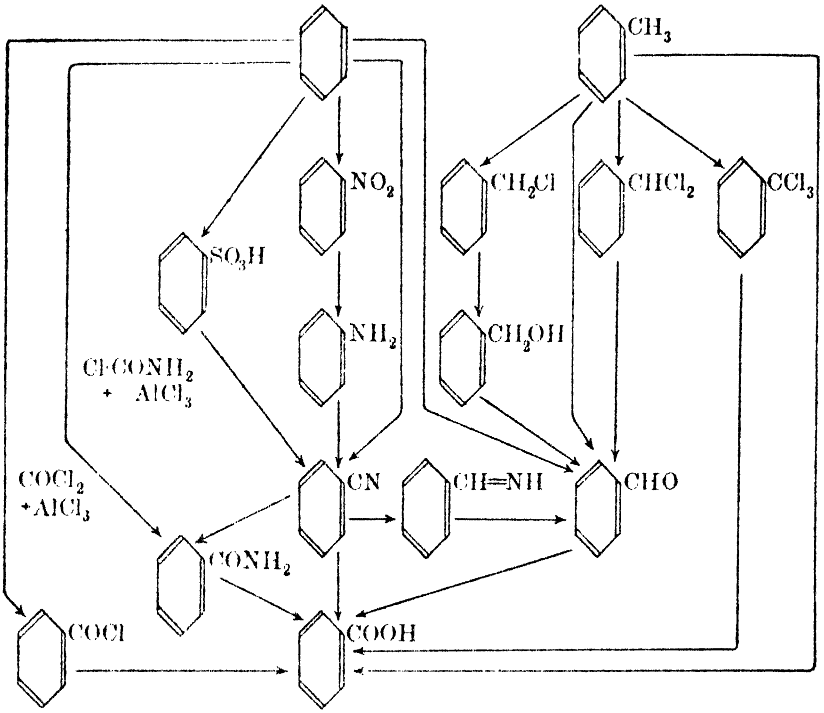
[2] Shipley, Fry and Price, *Rec. Trav. Chim.*, 1931, **50**, 1060.

[3] Tischtchenko, *Zentr.*, 1906, II, 1309 ; Child and Adkins, *J.A.C.S.*, 1923, **45**, 3013 ; 1925, **47**, 806.

[4] Gautier and Frolich, *Ann.*, 1880, **202**, 288.

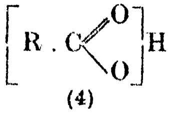
The hydrolysis of aromatic nitriles is often difficult—especially *para*-dinitriles such as terephthalic nitrile and its derivatives, and for this purpose 30–50 per cent. sulphuric acid is used. Hydrolysis of nitriles is not widely used as a preparative method in aliphatic chemistry, since the acid is usually more freely available than its nitrile; on the other hand, the use of the diazo compound with potassium cuprocyanide affords, in aromatic chemistry, an easy means of introducing the —CN group into positions where it would be difficult to obtain a carboxyl group by alternative means. In this way, it is possible to use the process of nitrile saponification as a synthetic measure. In Table II are shown in outline typical stages in the formation of aromatic acids. The table includes methods such as the use of the Friedel and Crafts reaction for introducing the —CO . NH$_2$, and —COCl group with carbamic chloride and carbonyl chloride respectively, in the presence of anhydrous aluminium chloride. This reaction has already been discussed (p. 217).

TABLE II



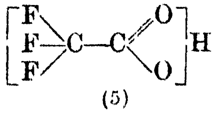
General Properties of Organic Acids

Acidity.—The structure of organic acids appears to offer some analogy with that of the organic sulphur acids and may be depicted as in (4 and 5); the degree



$$\left[R\,.\,C\begin{matrix}\nearrow O\\ \searrow O\end{matrix}\right]H$$

(4)



$$\left[\begin{matrix}F\\F\\F\end{matrix}\!\!>C—C\begin{matrix}\nearrow O\\ \searrow O\end{matrix}\right]H$$

(5)

of dissociation and the pH of solutions of acids depends largely on the nature of R in the formula (4); in the simple aliphatic acids the acidity decreases as the series is ascended, formic acid being exceptionally strong; on the other

TABLE III

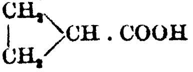
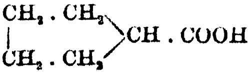
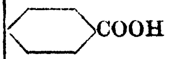
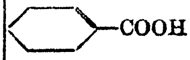
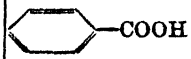
Acid	Formula	Dissociation constant $K \times 10^5$
Formic	$H . COOH$	21·4
Acetic	$CH_3 . COOH$	1·75
Propionic	$C_2H_5 . COOH$	1·34
n-Butyric	$C_3H_7 . COOH$	1·51
iso-Butyric	$(CH_3)_2CH . COOH$	1·5
n-Valeric	$C_4H_9 . COOH$	1·61
iso-Valeric	$(CH_3)_2CH . CH_2COOH$	1·7
Trimethylacetic	$(CH_3)_3C . COOH$	0·9
Caproic	$C_5H_{11}COOH$	1·4
Dimethyl ethyl acetic	$C_2H_5C(CH_3)_2COOH$	0·9
n-Heptylic	$C_6H_{13}COOH$	1·3
n-Caprylic	$C_7H_{15}COOH$	1·4
Fluoroacetic	FCH_2COOH	200
Difluoroacetic	$F_2CH . COOH$	5700
Trifluoroacetic	$F_3C . COOH$	50,000
Chloroacetic	$ClCH_2 . COOH$	150
Dichloroacetic	$Cl_2CH . COOH$	500
Trichloroacetic	$Cl_3C . COOH$	3000
Bromoacetic	$BrCH_2 . COOH$	150
Iodoacetic	$ICH_2 . COOH$	75
α-Chloropropionic	$CH_3 . CHClCOOH$	140
β-Chloropropionic	$CH_2Cl . CH_2 . COOH$	10
α-Bromopropionic	$CH_3 . CHBr . COOH$	108
β-Bromopropionic	$CH_2Br . CH_2 . COOH$	10
α-Iodopropionic	$CH_3 . CHI . COOH$	60
β-Iodopropionic	$CH_2I . CH_2 . COOH$	9
β-Nitropropionic	$CH_2(NO_2) . CH_2COOH$	10
α-Chlorobutyric	$CH_3 . CH_2 . CHCl . COOH$	140
β-Chlorobutyric	$CH_3 . CHCl . CH_2 . COOH$	9
γ-Chlorobutyric	$CH_2Cl . CH_2 . CH_2 . COOH$	3
α-Bromobutyric	$CH_3 . CH_2 . CHBr . COOH$	100
γ-Bromobutyric	$CH_2Br . CH_2 . CH_2 . COOH$	2·6
Acrylic acid	$CH_2{=}CH . COOH$	5·6
Trichloroacrylic	$CCl_2{=}CCl . COOH$	7000
Vinyl acetic	$CH_2{=}CH . CH_2 . COOH$	4·5
Crotonic acid	$CH_3 . CH{=}CH . COOH$ (*trans*)	2·4
iso-Crotonic	$CH_3 . CH{=}CH . COOH$ (*cis*)	4
α-Chlorocrotonic	$CH_3 . CH{=}CCl . COOH$ (*trans*)	70
α-Chloro *iso*-crotonic	$CH_3 . CH{=}CCl . COOH$ (*cis*)	160
Pentene-3-acid	$CH_3 . CH{=}CH . CH_2 . COOH$	3·3
Angelic	$CH_3 . CH{=}C(CH_3)COOH$ (*cis*)	5
Tiglic	$CH_3CH{=}C(CH_3)COOH$ (*trans*)	0·9
Methyl propiolic	$CH_3 . C{\equiv}C . COOH$	250
*cyclo*propanecarboxylic		1·4
*cyclo*Pentanecarboxylic		1·24
*cyclo*Hexanecarboxylic		1·3
*cyclo*Hexene-1-carboxylic		2·2
Benzoic acid		6·8
o-Fluorobenzoic	$F . C_6H_4 . COOH$	30
m-Fluorobenzoic	$F . C_6H_4 . COOH$	14

TABLE III—(*Continued*)

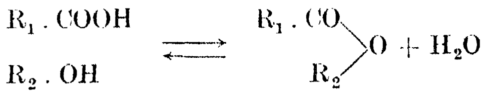
Acid	Formula	Dissociation constant K × 10^5	
p-Fluorobenzoic	$F . C_6H_4 . COOH$	14	
o-Chlorobenzoic	$Cl . C_6H_4 . COOH$	130	
m-Chlorobenzoic	$Cl . C_6H_4 . COOH$	150	
p-Chlorobenzoic	$Cl . C_6H_4 . COOH$	7	
o-Bromobenzoic	$Br . C_6H_4 . COOH$	140	
m-Bromobenzoic	$Br . C_6H_4 . COOH$	15	
o-Iodobenzoic	$I . C_6H_4 . COOH$	140	
m-Iodobenzoic	$I . C_6H_4 . COOH$	1·6	
o-Iodosobenzoic	$IO . C_6H_4 . COOH$	0·06	
o-Nitrobenzoic	$NO_2 . C_6H_4 . COOH$	620	
m-Nitrobenzoic	$NO_2 . C_6H_4 . COOH$	34	
p-Nitrobenzoic	$NO_2 . C_6H_4 . COOH$	40	
2, 6-Dinitrobenzoic	$(NO_2)_2C_6H_3 . COOH$	8100	
3, 5-Dinitrobenzoic	$(NO_2)_2C_6H_3 . COOH$	160	
Phenyl propionic	$C_6H_5 . CH_2 . CH_2 . COOH$	2·2	
Cinnamic	$C_6H_5 . CH=CH . COOH$ *trans-*	3·7	
	cis-	14	
Phenyl propiolic	$C_6H_5 . C \equiv C . COOH$	590	
		K_1	K_2
Oxalic	$(COOH)_2$	3800	—
Malonic	$CH_2(COOH)_2$	177	0·437
Succinic	$HOOC . (CH_2)_2 . COOH$	7·4	0·450
Glutaric	$HOOC . (CH_2)_3 . COOH$	4·6	0·534
Adipic	$HOOC . (CH_2)_4 . COOH$	3·9	0·529
Pimelic	$HOOC . (CH_2)_5 . COOH$	3·3	0·487
Suberic	$HOOC . (CH_2)_6 . COOH$	3	0·471
Azelaic	$HOOC . (CH_2)_7 . COOH$	2·8	0·464
Sebacic	$HOOC . (CH_2)_8 . COOH$	2·8	—

hand, introduction of halogen or nitro groups on to the carbon adjacent to the carboxyl causes a considerable increase in the dissociation constant and a much 'stronger' acid results. In the case of trifluoroacetic acid (5), the dissociation constant is nearly 30,000 times that for acetic acid itself. In Table III are set out the dissociation constants for a number of organic acids, from which the 'acid' nature of the nitro- or halogen- substituents is made strongly apparent. In the same way a triple bond acts as a powerful stimulant of acidity. Salt formation is characteristic of most of the organic acids, nearly all of which form a series of crystalline salts, the majority of alkali salts being soluble in water. In general, the sodium salt of an acid is more soluble in water than is the acid itself.

The hydroxyl group of the carboxyl is replaceable by halogens, giving rise to a series of acid halides which are to be dealt with in a later section of this chapter. In the same way acid anhydrides are formed by the loss of the elements of a molecule of water from two molecules of acid :—

$$\begin{matrix} R . COOH \\ R . COOH \end{matrix} \rightleftharpoons \left.\begin{matrix} R . CO \\ R . CO \end{matrix}\right\rangle O + H_2O$$

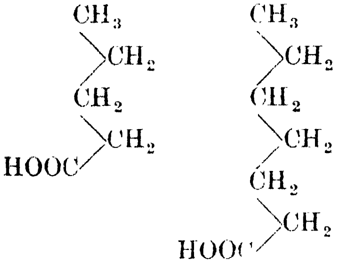
These also are discussed later in the chapter, as are the esters which constitute an anhydride type in which one member of the partnership is an acid and the other an alcohol ; the process of formation being analogous to the formation of anhydrides :—



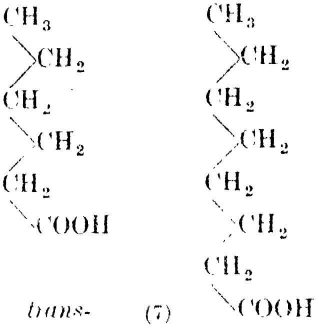
$$R_1.COOH + R_2.OH \rightleftharpoons R_1.CO{-}O{-}R_2 + H_2O$$

THE ALIPHATIC MONOBASIC ACIDS

Many of the aliphatic acids are to be found in plant and animal materials, either free or in the form of glycerides which constitute the large natural family of fats ; it is this association which gives rise to the term 'fatty acids' which has been applied to the series. In Table IV the general properties and occurrence of the straight chain acids are set out, and attention is drawn to the peculiar alternation of the melting points of the series ; it appears that the odd-carbon acids form a separate series with a range of melting points lower than those of the acids with an even number of atoms. Nekrassov [1] suggested, in 1927, that this was due to the formation of a static zig-zag molecule in the



cis- (6)



trans- (7)

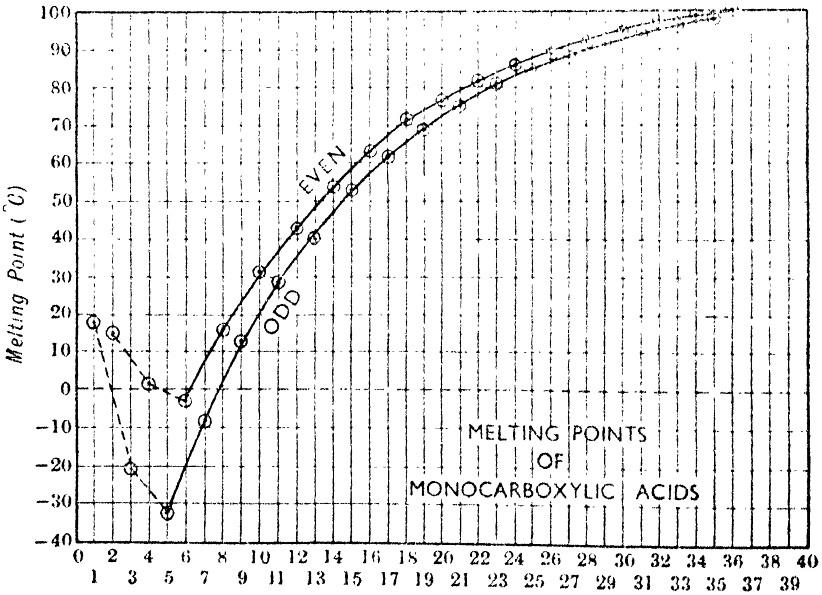


FIG. 1.

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[1] Nekrassov, *Z. Physikal. Chem.*, 1927, **128**, 303.

solid state which would have the effect of a pseudo *cis*- and *trans*- arrangement of the terminal groups, the odd-numbered acids (as in 6) having a *cis*- structure and the even-numbered acids (as in 7) a *trans*- form ; this hypothesis is in keeping with the facts (*a*) that the even-numbered acids melt higher than the next higher odd-numbered acid, (*b*) X-ray studies of the solid acids, and (*c*) observations made on the molecule-length from the study of thin films of the solid acids. The full implications of this alternation of melting point are shown in Fig. 1 opposite.

The phenomena is observed with other physical properties besides melting point, such as dielectric constant, surface tension and molecular volume. On the other hand, the two curves obtained with, for example, dielectric constant tend to approach one another and to become one curve as the temperature rises, especially above the melting point, this being attributed to the diminution of the resistance to free rotation. Table IV comprises a list of the straight chain aliphatic acids, and Table V a list of those with an arborescent structure ; in the latter table only the more common acids are described.

Some Individual Aliphatic Acids

Formic Acid.—Whilst, during the seventeenth and eighteenth centuries, it had been fairly well established that an acid could be obtained from ants and other insects by distillation with water, the product was confused with the acetic acid of vinegar, and although Margraaf in 1749 put forward the theory that the acid of ants was a substance distinct from acetic acid, this was denied ; even as late as 1802 Fourcroy and Vauquelin stated that the so-called formic acid was merely a mixture of malic and acetic acids. Gehlen, in 1810, disposed of this fallacy, and the work of Döbereiner, in 1822, on the artificial preparation of the acid by oxidation of tartaric acid led to a more plentiful supply, and to a closer examination of its properties.

The earliest artificial means of preparation of formic acid consisted of oxidising carbohydrate material with manganese dioxide and sulphuric acid. The method of Liebig was to heat a suspension of starch with about four times its weight of manganese dioxide and three parts of sulphuric acid. Formic acid distilled over. This method was abandoned when it was found that a better yield of formic acid could be obtained from heating oxalic acid mixed with crushed quartz sand :—

$$(COOH)_2 \longrightarrow H\,.\,COOH + CO_2$$

The yield is poor, however, and it is interesting to reflect that the relatively plentiful supplies of formic acid obtainable by alternative methods (see below) are now used to produce oxalic acid industrially by a method which is to a large extent the reverse of the reaction just described, namely, the action of heat on sodium formate :—

$$2H\,.\,COONa \longrightarrow (COONa)_2 + H_2.$$

The yield of formic acid from oxalic acid is increased by using the improved method of Berthelot, in which glycerol and oxalic acid are heated together.

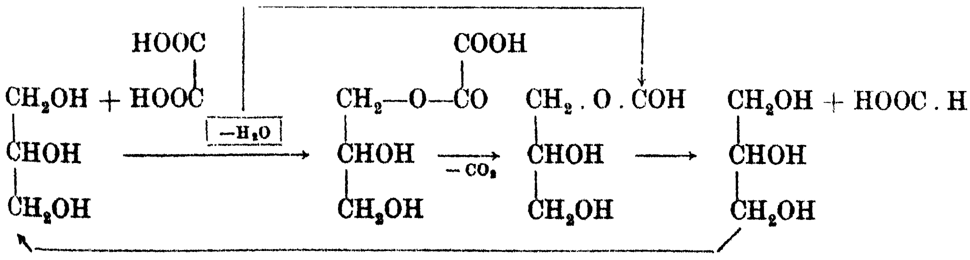


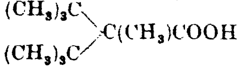
TABLE IV

Formula	Name of acid	Carbon atoms	Even		Odd		B.P.	Source
			M.P.	Δt°	M.P.	Δt°		
$H . COOH$	Formic	1	8·3°				101°	Red ants, nettles, animal tissues
$CH_3 . COOH$	Acetic	2			16·5°		118·2°	Nearly all plant and animal tissues
$CH_3 . CH_{22}COOH$	Propionic	3	— 21°	— 29·3°			141·3°	*Gingko biloba* fruits, and in fungi (agaric); sweat
$CH_3(CH_2)COOH$	Butyric	4			2°	14·5°	164°	Free in common tansy; as esters in parsnip, fruits and in *Heracleum giganteum*
$CH_3(CH_2)_3COOH$	Valeric	5	— 34·5°	— 13·5°			186°	
$CH_3(CH_2)_4COOH$	Caproic	6			— 4°	— 6°	205°	Butter, palmarosa oil, oil of parsnip, etc., coconut oil
$CH_3(CH_2)_5COOH$	Heptoic	7	— 9°	+ 25·5°			223°	Calamus oil
$CH_3(CH_2)_6COOH$	Caprylic	8			16°	+ 20°	237°	Butter, coconut oil and wine (as ester)
$CH_3(CH_2)_7COOH$	Pelargonic	9	12·5°	+ 21·5°			252°	Pelargonium (geranium) leaves; japan wax (as ester)
$CH_3(CH_2)_8COOH$	Capric	10			31·5°	+ 15·5°	269°	Butter, Limburg cheese, coconut and palm kernel oils (as ester)
$CH_3(CH_2)_9COOH$	Undecylic	11	29·5°	+ 17°			212° 100 mm.	Not found naturally
$CH_3(CH_2)_{10}COOH$	Lauric	12			43·5°	+ 12°	225°/100 mm.	Laurel wax, coconut oil, spermaceti, pichurium beans
$CH_3(CH_2)_{11}COOH$	Tridecylic	13	41·5°	+ 12°			236°/100 mm.	In iris extracts, and by the oxidation of sphingosine
$CH_3(CH_2)_{12}COOH$	Myristic	14			54°	+ 10·5°	248°/100 mm.	Nutmeg fat, myrtle wax, coconut and palm kernel oils
$CH_3(CH_2)_{13}COOH$	Pentadecylic	15	53°	+ 11·5			257°/100 mm.	Not found naturally

$CH_3(CH_2)_{14}COOH$	Palmitic	16			63°	+ 9°	268°/100 mm.	Very widely distributed in all plants, both free and as the glyceride
$CH_3(CH_2)_{15}COOH$	Margaric	17	62°	+ 9°			277°/100 mm.	*Datura Stramonium* seeds and in pork fat
$CH_3(CH_2)_{16}COOH$	Stearic	18			70·5°	+ 7·5°	287°/100 mm.	Cocoa-butter, shea butter, animal fats generally
$CH_3(CH_2)_{17}COOH$	Nonadecylic	19	69·5°	+ 7·5°			298°/100 mm.	Synthetic only
$CH_3(CH_2)_{18}COOH$	Arachidic	20			76°	+ 5·5°	205°/10 mm.	Free in cascara stalks, in olive oil, ground nut and macassar oils
$CH_3(CH_2)_{19}COOH$	Heneicosoic	21	75·5°	+ 6°				Synthetic
$CH_3(CH_2)_{20}COOH$	Behenic	22			80·5°	+ 4·5°		Ben oil (*Moringa* species), colza, rice and cottonseed oils
$CH_3(CH_2)_{21}COOH$	Tricosoic	23	80·5°	+ 5°				Synthetic
$CH_3(CH_2)_{22}COOH$	See App. IV for modern conceptions concerning the nature of higher aliphatic acids.	24			85°	+ 4·5°		Peanut oil, Carnaüba wax, mould fat, beechwood tar
$CH_3(CH_2)_{23}COOH$		25	83·5°	+ 3°				Synthetic
$CH_3(CH_2)_{24}COOH$		26			88°	+ 3°		Carnaüba. poppy wax, beeswax, and sheep sweat
$CH_3(CH_2)_{25}COOH$		27	87·5°	+ 4°				
$CH_3(CH_2)_{26}COOH$		28			91°	+ 3°		
$CH_3(CH_2)_{27}COOH$		29	91°	+ 3·5°				Montan wax
$CH_3(CH_2)_{28}COOH$		30			93·5°	+ 3·5°		Carnaüba and beeswax
$CH_3(CH_2)_{29}COOH$		31	94°	+ 3°				
$CH_3(CH_2)_{30}COOH$		32			96°	+ 2·5°		Plant lice (*Psylla ani*)
$CH_3(CH_2)_{31}COOH$		33	96·2°	+ 2·2°				Plant lice (*Psylla ani*)
$CH_3(CH_2)_{32}COOH$	Tetratriacontanoic	34			98·4°	+ 2·4°		
$CH_3(CH_2)_{33}COOH$	Pentatriacontanoic	35	98·4°	+ 2·2°				
$CH_3(CH_2)_{34}COOH$	Hexatriacontanoic	36			100·2°	+ 2·2°		

TABLE V

BRANCHED CHAIN ALIPHATIC ACIDS

No. of C atoms	Name of acid	Formula	M.P.	B.P.	Source
4	Isobutyric 2-Methylpropane acid	$(CH_3)_2CH\,.\,COOH$	$-46°$	155°	Arnica, leaves of *Anthemis nobilis* and the *Fritillaria imperialis*
5	2-Methylbutane acid	$CH_3\,.\,CH_2CH(CH_3)COOH$	—	177°	*Ipomea* resins, volatile oils obtained during coffee roasting
5	Isovaleric acid 3-Methylbutane acid	$(CH_3)_2CH\,.\,CH_2\,.\,COOH$	-30	176·5°	Valerian, oils of *Delphinus phocena* and *Delphinus globiceps*
5	Pivalic acid 2, 2-Dimethylpropane acid	$(CH_3)_3C\,.\,COOH$	$+35°$	70°/14 mm.	Synthetic
6	2-Methylpentane acid	$CH_3\,.\,CH_2\,.\,CH_2\,.\,CH(CH_3)COOH$	—	194°	
6	3-Methylpentane acid	$CH_3\,.\,CH_2\,.\,CH(CH_3)CH_2\,.\,COOH$	$-42°$	197°	
6	4-Methylpentane acid	$(CH_3)_2\,.\,CH\,.\,CH_2\,.\,CH_2\,.\,COOH$	$-33°$	200°	
6	2-Ethylbutane acid	$(C_2H_5)_2\,.\,CH\,.\,COOH$	$-32°$	193°	
6	2, 2-Dimethylbutane acid	$C_2H_5\,.\,C(CH_3)_2COOH$	$-15°$	187	
6	2, 3-Dimethylbutane acid	$(CH_3)_2\,.\,CH\,.\,CH(CH_3)COOH$	$-15°$	192°	
6	3, 3-Dimethylbutane acid	$(CH_3)_3\,.\,C\,.\,CH_2\,.\,COOH$	$+5·6°$	184	
8	Di-*iso*propylacetic acid	$((CH_3)_2CH)_2CH\,.\,COOH$	—	219°	
9	*iso*-Pelargonic 2-Methyloctane acid	$CH_3(CH_2)_5CH(CH_3)COOH$	—	140°/15 mm.	A characteristic acid of hops
10	Tetrahydrogeranic acid 3, 6-Dimethyloctane acid	$(CH_3)_2\,.\,CH(CH_2)_3\,.\,CH(CH_3)CH_2\,.\,COOH$	—	134°/10 mm.	From reduction of geranic acid
11	Methyl-*bis*-(ter-butyl) acetic acid	 $\begin{matrix}(CH_3)_3C\\(CH_3)_3C\end{matrix}\!\!>C(CH_3)COOH$	68	257°	From the chromic oxidation of wool pigments
16	Isopalmitic 14-Methylpentadecylic acid	$(CH_3)_2CH\,.\,(CH_2)_{12}COOH$	61-62°	—	Synthetic
18	Isostearic 16-Methylheptadecylic acid	$(CH_3)_2CH\,.\,(CH_2)_{14}COOH$	68°	—	
19	2-Methyloctadecylic acid	$CH_3\,.\,(CH_2)_{15}CH(CH_3)COOH$	58°	—	

The formulæ on page 481 indicate the course of the reaction in which it appears that glyceryl oxalate is formed by loss of the elements of water from glycerol and oxalic acid. This readily parts with carbon dioxide to give glyceryl formate which is split to glycerol and formic acid by the water from the esterification of glycerol with fresh oxalic acid ; the glycerol is, therefore, part of a regenerative cycle and can serve for the preparation of considerable quantities of formic acid.

The process now used almost exclusively for the production of formates and of formic acid is that originally described by Berthelot [1] and improved by Merz and Tibiricá.[2] Berthelot described the interaction of carbon monoxide and potassium hydroxide to give potassium formate, whilst Merz and his colleague showed that the reaction proceeded more easily with sodium hydroxide in the presence of a little lime. The process has had to wait for its industrial development until such time as chemical engineering technique has become capable of handling reactions between gases and solids under pressure. In the present-day preparation of formic acid, carbon monoxide is allowed to react with coarsely granular sodium hydroxide in autoclaves at 120–150° and 6–8 atmospheres. The absorption to form sodium formate is almost quantitative and the material needs but one recrystallisation to give a sodium formate of good quality.

The production of concentrated formic acid is a matter of some difficulty ; since the raw material available for its preparation is sodium formate it follows that the acid must be liberated by another acid, of greater strength. Sulphuric acid is usually the acid of choice in such cases, but its use in this particular case is contra-indicated by the fact that it readily decomposes formic acid to carbon monoxide and water ; on the other hand, dilute sulphuric acid would give a dilute formic acid which can only be concentrated by distillation to a strength of 77 per cent. at which point it forms a constant boiling mixture with water. By using cold concentrated sulphuric acid it is possible to obtain a good yield of concentrated formic acid, provided the sulphuric acid is diluted with anhydrous formic acid during use. Thus, 400 kg. of sodium formate are gradually added to a cooled mixture of 400 kg. anhydrous formic acid and 300 kg. of sulphuric acid, at such a rate that the temperature does not rise above 30°. The sodium sulphate separates out and crude 97 per cent. formic acid can be decanted and distilled with a little anhydrous oxalic acid. In this way about 600 kg. of anhydrous formic acid can be recovered.

Formic acid frequently forms a product of the decomposition of organic substances and there are numerous reactions in which it appears as an end-product. The more interesting of these are mentioned below :—

1. Carbon disulphide is heated with water and iron at 100° ; ferrous formate is produced :—

$$2CS_2 + 4H_2O + 2Fe \longrightarrow (H\,.\,COO)_2Fe + FeS + 3H_2S.$$

2. The action of hydrolytic agents on hydrocyanic acid yields formic acid, the former being, therefore, considered the nitrile of the latter :—

$$HCN + 2H_2O \longrightarrow H\,.\,COONH_4 \longrightarrow H\,.\,COOH.$$

3. The direct combination of carbon dioxide and hydrogen under the influence of a silent discharge yields formic acid

$$CO_2 + H_2 \longrightarrow H\,.\,COOH.$$

4. The reduction of carbonates or of carbon dioxide frequently yields formic acid or formates, as, for example, the action of moist carbon dioxide on potassium, or that of sodium amalgam on ammonium carbonate.

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[1] Berthelot, *Ann.*, 1859, **97**, 125.

[2] Merz and Tibiricá, *Ber.*, 1877, **10**, 2117 ; 1880, **13**, 23.

5. The hydrolysis of chloroform and of chloral, also yields formic acid

$$HCCl_3 + 3NaOH \longrightarrow H.C(OH)_3 + 3NaCl \longrightarrow H.COOH + H_2O$$
$$CCl_3.CHO + NaOH \longrightarrow CHCl_3 + H.COONa.$$

It may be added that in the pressure synthesis of methanol from carbon monoxide and hydrogen an appreciable amount of methyl formate is formed :—

$$2CO + 2H_2 \longrightarrow H.COOCH_3$$

which constitutes a potential source of formic acid.

The physical properties of formic acid are unusual in that it exists at ordinary temperatures mainly as a dimer, gives an azeotrope with 22·5 per cent. of water which boils at a temperature (107°) higher than the b.p. of either component, and constitutes a strongly dissociating solvent ; solutions of sodium formate in anhydrous formic acid are nearly 90 per cent. dissociated. It is this factor that enables the decomposition of sodium formate by sulphuric acid to take place so readily.

Chemically, formic acid may be regarded as an aldehyde as well as an acid, HO . CHO, and whilst the acidic properties are evidenced in the usual way, the aldehydic properties are also well marked. Thus, formic acid is an antiseptic of a nature similar to formaldehyde, and yields an oxime with hydroxylamine, HO . CH=NOH. It also reacts as a powerful reducing agent ; it reduces mercuric to mercurous chloride ; and liberates gold, silver and platinum as the metal, from their salts. This activity is the basis of Fulmer's process for the analytical separation of copper and cadmium, the latter being unaffected by potassium formate at 160°, whilst the former is reduced to the metal.

A valuable reducing activity of anhydrous formic acid is its ability to convert the higher aliphatic acids to their aldehydes [1]

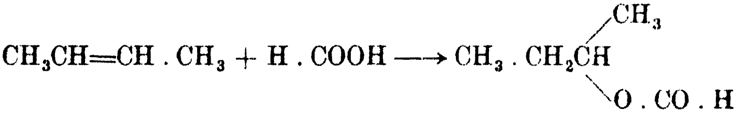
$$CH_3(CH_2)_nCOOH + HCOOH \longrightarrow CH_3(CH_2)_nCHO + CO_2 + H_2O.$$

In the same way triphenylcarbinol derivatives are reduced to triphenylmethane compounds [2]

$$(C_6H_5)_3C.OH + H.COOH \longrightarrow (C_6H_5)_3CH + CO_2 + H_2O.$$

Conversely, the reduction of formic acid itself is difficult to accomplish ; magnesium powder gives a little formaldehyde, and the reaction enables small quantities of formic acid to be detected analytically.[3]

Hydrazine reacts readily with formic acid to give the monoformhydrazide, H . CO . NH . NH$_2$, and not the hydrazone, HO . CH=N . NH$_2$, according to Pelizzeri,[4] but the two substances may be tautomeric. Formic acid also exhibits a tendency to add across a double bond and with hydrocarbons such as butene



$$CH_3CH{=}CH.CH_3 + H.COOH \longrightarrow CH_3.CH_2CH\begin{matrix}\diagup CH_3 \\ \diagdown O.CO.H\end{matrix}$$

gives formic esters, from which the corresponding alcohol may be prepared by hydrolysis.

Reference has already been made to the decomposition of formic acid by hot concentrated sulphuric acid ; this decomposition affords a convenient method of preparing carbon monoxide for laboratory purposes, a stream of 80 per cent. formic acid being allowed to drop into the hot sulphuric acid ; decomposition at 110–130° is almost instantaneous and the carbon monoxide is free from most impurities.

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[1] Sabatier and Maihle, *C.R.*, 1912, **154**, 562.

[2] Kovache, *Ann. Chim.*, 1918 [9] **10**, 184.

[3] Fenton, *J.C.S.*, 1907, **91**, 690.

[4] Pelizzeri, *Gazz. Chim. Ital.*, 1894, **2411**, 225 ; 1909, **39-1**, 529.

Formic acid, being cheap, has a wide industrial application ; it has a very pronounced antiseptic action, and is used abroad for the preservation of fruit and fruit-juices ; in brewing for keeping down secondary fermentations and for the disinfection of vats and casks ; the wine industry also employs formic acid in this capacity. Tanneries use it in deliming hides. Most of the formic acid used industrially is consumed in dyeing where it is invaluable for replacing the more expensive organic acids in the dyebath, and acting as a levelling agent ; the main use of the salts of formic acid is the conversion of sodium formate to sodium oxalate on heating, a process which gives rise to the bulk of the oxalic acid and oxalates of commerce.

No anhydride of formic acid is known ; but a mixed anhydride with acetic acid can be prepared by the decomposition of acetic anhydride by formic acid :—

$$(CH_3CO)_2O + HCOOH \longrightarrow CH_3CO . O . CHO + CH_3COOH.$$

Acetic Acid.—The formation of vinegars, or products of fermentation containing about 4 per cent. of acetic acid has been known from very early times. Vinegar was formerly prepared by the acetic fermentation of wine, a slow process which produced vinegar of a characteristic and desirable bouquet. It was, however, especially when carried out by the Orleans process, a slow operation. The process was speeded up by pumping the dilute alcoholic liquor over a large mass of shavings on which the organism (*Mycoderma aceti*) is spread ; the large surface exposed together with the constant movement of the liquid causes the fermentation to be complete in a few hours. Cider and wort from the washing of malt are used in this country for vinegar manufacture ; neither gives a vinegar of such good bouquet as that from wine, which is richer in esters.

The highest concentration of acetic acid procurable by fermentation is 14–15 per cent., but this is unusual, the standard strength for domestic vinegar being 4–5 per cent. The earliest specimens of concentrated acetic acid were obtained by neutralising vinegar with soda or lime and evaporating the solution to dryness ; the acetic acid was then obtained by distillation of the salt with concentrated sulphuric acid.

Lavoisier[1] first recognised that the acetic acid of vinegar was the product of oxidation of ethanol ; he was also able to show that the change could be brought about by inorganic oxidising agents. The true nature of the change and the amount of oxygen necessary to complete it were ascertained by Dobereiner in 1822.[2]

Acetic acid is widely distributed free, or combined as salts or esters, in natural structures ; it occurs free or as the calcium or potassium salt in most plant juices. Nearly all animal fluids contain traces of acetic acid, and it is found as octyl acetate in *Heracleum giganteum* ; triacetin, its glyceryl ester, is found in the seeds of *Croton tiglium* and the oil of the fruit of the spindle tree, *Euonymus europeus*.

It was soon realised that the aqueous condensate from the destructive distillation of wood contained a considerable proportion of acetic acid, and this liquid, the so-called ‘ Pyroligneous ’ acid, constituted the chief source of industrial acetic acid for many years. The crude acid was neutralised with soda and evaporated to dryness ; the residue, dark-brown or black, was calcined to remove tar and empyreumatic material ; this residue, ‘ grey acetate ’, was the starting point for all acetic acid and its derivatives.

Recent years have seen the development of large-scale processes by which acetylene from calcium carbide is converted to acetic acid. This is usually accomplished in two stages, the first being the conversion of acetylene to acetaldehyde by sulphuric acid containing water and mercuric salts (see p. 111)

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[1] Lavoisier, *Traité de chimie élémentaire* (Paris), 1789, **1**, 159.

[2] Dobereiner, *Schweig. J.*, 1822, **54**, 416.

$$CH{\equiv}CH + H_2O \longrightarrow CH_3\,.\,CHO + \tfrac{1}{2}O_2 \longrightarrow CH_3COOH$$

followed by treatment of the acetaldehyde with air in the presence of a catalyst-mass of manganese acetate supported on inert material. By using a compound catalyst it is possible to complete the transformation in one stage; but the majority of large-scale plants use the two-stage process.

Besides the methods mentioned above, acetic acid is obtained by the oxidation of an enormous variety of organic substances, by the hydrolysis of acetonitrile; especially interesting is Kolbe's 'total synthesis' of acetic acid, carried out in 1843–44 at a time when the synthesis of natural products of animal and vegetable origin was discrediting the theory of 'vitalism'. The stages are evident from the formulæ:—

$$\begin{array}{ll}
\text{(i)} & C + S_2 \longrightarrow CS_2, \\
\text{(ii)} & CS_2 + 3Cl_2 \xrightarrow{Fe} CCl_4 + S_2Cl_2, \\
\text{(iii)} & 2CCl_4 \longrightarrow C_2Cl_4 + 2Cl_2, \\
\text{(iv)} & C_2Cl_4 + 2H_2O + Cl_2 \longrightarrow CCl_3\,.\,COOH + 3HCl, \\
\text{(v)} & CCl_3COOH + 3H_2 \longrightarrow CH_3COOH + 3HCl,
\end{array}$$

the last stage was accomplished by the use of potassium amalgam, a reaction which had previously been investigated by Melsens.

Acetic acid exists mainly as a dimer, m.p. 16·55°.[1] Acetic acid mixes in all proportions with water, alcohol and ether, but not with carbon bisulphide. The partition coefficients of acetic acid between water and many solvents are known; and they substantiate the industrially accepted fact that *iso*propyl ether is the best medium for recovering acetic acid from its aqueous solutions.[2]

Pure glacial acetic acid shows no trace of acid properties; it can be kept sealed in a tube with dry marble indefinitely, and its solution in absolute alcohol or nitrobenzene is non-conducting. Neither solution has any effect on an anhydrous carbonate; on the other hand, a solution of potassium acetate in absolute alcohol is decomposed by dry carbon dioxide, potassium carbonate being precipitated and acetic acid remaining in solution.

Acetic acid demonstrates a stability such that the most energetic measures are required for its decomposition. It can be decomposed by ultra-violet irradiation[3] giving a mixture of gases in which approximately one-third is a mixture of methane and ethane. Heat alone, on the other hand, has little effect on acetic acid; it is but little changed by passage through a glass tube at red heat, although at 1000° it is decomposed, giving a mixture of methane, ethylene, carbon dioxide and acetic anhydride. In the presence of metals the decomposition sets in at a much lower temperature; copper and nickel induce the formation of methane and carbon dioxide at 400°; alumina and thoria give substantial quantities of acetone:—

$$2CH_3COOH \longrightarrow CH_3COCH_3 + H_2O + CO_2.$$

The oxidation of acetic acid is only achieved with that difficulty to be expected with a substance, itself a 'final' product of the oxidation of many other organic substances. Ferric nitrate oxidises it to formalhehyde;[4] alkaline permanganate oxidises it slowly in the cold to oxalic acid; of the chromates only one, that of silver, oxidises it rapidly to carbon dioxide and water; the others react but slowly.

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[1] The value of Timmermans and Hennaut-Roland is given, *J. Chim. Phys.*, 1930, **27**, 401; higher values have been quoted, but on less substantial evidence.

[2] Smith and Elgin, *J. Phys. Chem.*, 1935, **39**, 1149.

[3] Berthelot and Gaudechon, *C.R.*, 1910, **151**, 479; 1913, **156**, 70.

[4] Beurath, *J. Pr. Chem.*, 1911, 2, **84**, 325.

Apart from conversion to esters, acetic acid is mainly used as a solvent, as a source for its chloride and anhydride, and as an acetylating agent. Its most important synthetic reaction is its condensation[1] with aldehydes and ketones to give unsaturated acids—Perkin's reaction (see p. 393). Few of the acetates call for detailed consideration, although an exception must be made for lead tetra-acetate, made by dissolving red lead in warm acetic acid.[2]

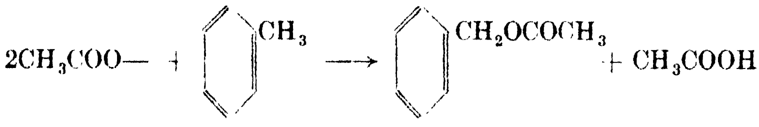
Lead tetra-acetate[3] tends to decompose :—

$$Pb(OCOCH_3)_4 \longrightarrow Pb(OCOCH_3)_2 + 2CH_3\,.\,CO\,.\,O—$$

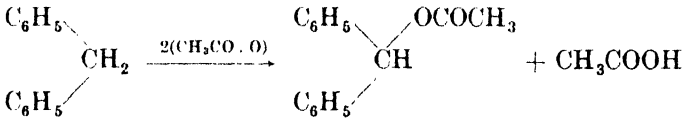
giving normal lead acetate and two acetic moieties which endeavour to achieve saturation by one or other of the following processes :—

(1) Acquisition of a hydrogen atom :—

(*a*) From a hydrocarbon, *e.g.*, toluene, which is converted to benzyl acetate :—

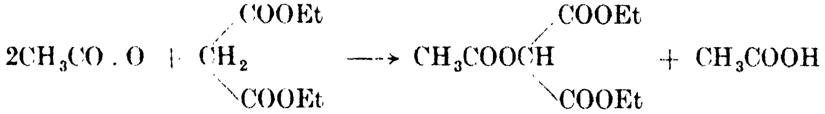


(*b*) The reaction is particularly successful with diphenylmethane and its analogues, which are converted to acetates, *e.g.*,

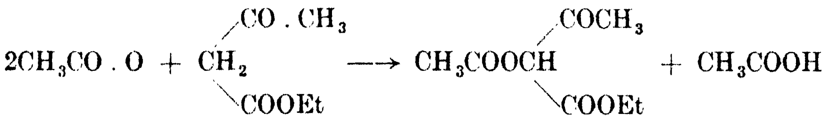


$$\begin{matrix} C_6H_5 \\ & CH_2 \\ C_6H_5 \end{matrix} \xrightarrow{2(CH_3CO\,.\,O)} \begin{matrix} C_6H_5 & & OCOCH_3 \\ & CH & \\ C_6H_5 & & \end{matrix} + CH_3COOH$$

(*c*) The hydrogen from an active methylene group also reacts readily, as indicated below with malonic and acetoacetic esters



$$2CH_3CO\,.\,O + CH_2\begin{matrix} COOEt \\ COOEt \end{matrix} \longrightarrow CH_3COOCH\begin{matrix} COOEt \\ COOEt \end{matrix} + CH_3COOH$$

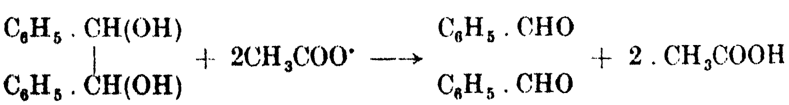


$$2CH_3CO\,.\,O + CH_2\begin{matrix} CO\,.\,CH_3 \\ COOEt \end{matrix} \longrightarrow CH_3COOCH\begin{matrix} COCH_3 \\ COOEt \end{matrix} + CH_3COOH$$

(2) Valency relations can be restored by the addition of the two acetate moieties to a double bond, thus producing the diacetate of a glycol :—

$$C_2H_4 + 2CH_3COO^{\cdot} \longrightarrow CH_3COO\,.\,CH_2CH_2\,.\,OCOCH_3$$

(3) The action of lead tetra-acetate upon glycols is to oxidise them to aldehydes or ketones with fragmentation of the molecule, e.g., hydrobenzoin is almost quantitatively oxidised to benzaldehyde



$$\begin{matrix} C_6H_5\,.\,CH(OH) \\ | \\ C_6H_5\,.\,CH(OH) \end{matrix} + 2CH_3COO^{\cdot} \longrightarrow \begin{matrix} C_6H_5\,.\,CHO \\ \\ C_6H_5\,.\,CHO \end{matrix} + 2\,.\,CH_3COOH$$

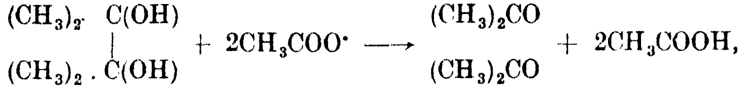
---

[1] Perkin, *J.C.S.*, 1877, **31**, 389.

[2] Dimroth and Schweizer, *Ber.*, 1923, **56**, 1375.

[3] Waters, 'Oxidations with Lead tetra-acetate', *Ann. Rep. Chem. Soc.*, 1945, **42**, 143.

In the same way pinacol gives acetone



$$\begin{array}{l}(CH_3)_2\cdot C(OH)\\ \quad\quad\;\,|\\ (CH_3)_2\,.\,C(OH)\end{array} + 2CH_3COO^{\bullet} \longrightarrow \begin{array}{l}(CH_3)_2CO\\ \\ (CH_3)_2CO\end{array} + 2CH_3COOH,$$

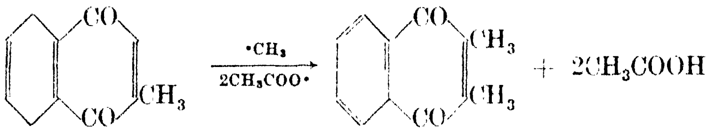
and ethyl glycerol, an aldehyde

$$C_2H_5OCH_2\,.\,CHOH\,.\,CH_2OH \xrightarrow{2CH_3COO} C_2H_5O\,.\,CH_2CHO + H\,.\,CHO + 2CH_3COOH$$

(4) At higher temperatures the acetate radicle may decompose with the formation of free methyl :—

$$CH_3\,.\,COO^{\bullet} \longrightarrow {}^{\bullet}CH_3 + CO_2$$

Fieser[1] has shown that this free radicle will methylate quinones, thus :—



This is a very unusual form of methylation.

These transformations are particularly valuable in the determination of structure.

Propionic Acid.—In 1844 Gottlieb[2] obtained a new acid by the distillation of sugar, starch and the substance ' metacetone ',* with potassium hydroxide. He called it ' metacetonic ' acid. The researches of Dumas, Leblanc and others[3] showed that the new acid could be obtained by the saponification of ethyl cyanide, and they named it ' propionic acid '. It is of somewhat limited natural occurrence—the sweat of animals, and particularly of humans suffering from rheumatic conditions,[4] and the fruits of *Gingka biloba* contain propionic acid ; it is a constant companion of acetic acid in nearly all acid fermentations. The bouquet of vinegar is attributable in part to small quantities of ethyl propionate formed during the fermentation. Methods of synthesis include :—

(1) Hydrolysis of the nitrile obtained from the direct combination of ethylene and hydrogen cyanide in presence of a catalyst. The hydrolysis can be done by steam in the presence of a contact mass

$$C_2H_4 + HCN \longrightarrow C_2H_5CN \xrightarrow{2H_2O} C_2H_5COOH + NH_3$$

This process is capable of industrial development, should large quantities of propionic acid become necessary.

(2) The action of carbon monoxide on sodium ethylate is another reaction that might be made the subject of research with a view to producing propionic acid in bulk.

$$CO + C_2H_5ONa \longrightarrow C_2H_5\,.\,COONa$$

The reaction proceeds at 190°, but would probably give high yields if conducted under pressure.[5]

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[1] Fieser and Chang, *J.A.C.S.*, 1942, **64**, 2043.

[2] Gottlieb, *Ann.*, 1844, **52**, 121.

[3] Dumas, Leblanc *et al.*, *C.R.*, 1847, **25**, 676 and 781 ; *Ann.*, 1846, **57**, 174.

[4] De Coninck, *C.R.*, 1912, **156**, 1272.

[5] Frölich, *Ann.*, 1880, **202**, 290.

* ' Metacetone ' was a mixture obtained by distilling sugar with quicklime. [Cf. Fischer and Laycock, *Ber.*, 1889, **22**, 101.]

(3) Oxidation methods are used for preparing the comparatively small amounts of propionic acid required industrially, the source being *n*-propyl alcohol, which on oxidation yields a mixture of propionaldehyde and propionic acid :—

$$CH_3CH_2CH_2OH \longrightarrow CH_3CH_2CHO \longrightarrow CH_3CH_2COOH$$

(4) Bost[1] obtained reasonable yields of propionic acid by the restricted fermentation of maize starch after malting.

(5) Propionic acid can also be obtained from the high pressure interaction of ethylene, carbon monoxide and water.

The characteristic odour of propionic acid lies between the sharp tang of acetic acid and the repulsive animal odours of the higher acids. As an acid it is much weaker than acetic acid, and it is thermally less stable, being decomposed to diethylketone at a temperature of 300° in the presence of suitable catalysts (zinc or cadmium). The reactive hydrogen atoms of propionic acid are those attached to the α-carbon atom ; they can be replaced by halogens and will take part in the Perkin reaction. The atoms of the terminal methyl group are hard to bring into reaction, but the carboxyl group of propionic acid is reactive quite apart from its hydrogen ionisation. Thus propionic and formic acid vapours passed together over titanium dioxide at 280–300° give a good yield[2] of propionaldehyde (propanal) :—

$$CH_3CH_2COOH + HCOOH \longrightarrow CH_3CH_2CHO + CO_2 + H_2O$$

The salts of propionic acid offer few points of general interest ; the basic lead salt is almost insoluble in water and offers a method of separation of acetic and propionic acids.

The Butyric Acids.—Chevreul[3] in his classical researches on the nature of fats, which forms the basis of our theories of saponification, isolated in 1814 three volatile acids from the products of saponification of butter. He named them butyric, caproic and capric acids and since his time butyric acid has been found in a wide variety of natural substances including other fats, animal fluids, including sweat, and in the fruits of various plants.

***n*-Butyric acid**, $CH_3CH_2CH_2COOH$, is best prepared by fermentation, although it can, of course, be obtained by the normal synthetic methods. The fermentation of sucrose in the presence of chalk, by *B. Butylicus* yields about 30 per cent. of *n*-butyric acid in the form of calcium butyrate from which the acid itself can be obtained readily by distillation with dilute sulphuric acid.

n-Butyric acid can also be produced in bulk by the catalytic oxidation of *n*-butyl alcohol with air. The acid is a liquid of overpowering and unpleasant rancid odour ; it is miscible with all proportions of water at ordinary temperatures, but can easily be salted out of its solutions by calcium chloride.

***iso*-Butyric acid** is best obtained by the direct oxidation of *iso*-butyl alcohol with chromic acid mixture when butyric acid mixed with a substantial proportion of *iso*-butyl-*iso*-butyrate is formed. On saponification the alkaline *iso*-butyrate is readily separated from the *iso*-butyl alcohol, and can be converted to the free acid by distillation with sulphuric acid. Unlike *n*-butyric acid it is not miscible with water in all proportions, requiring five volumes of water at 20° for complete solution.

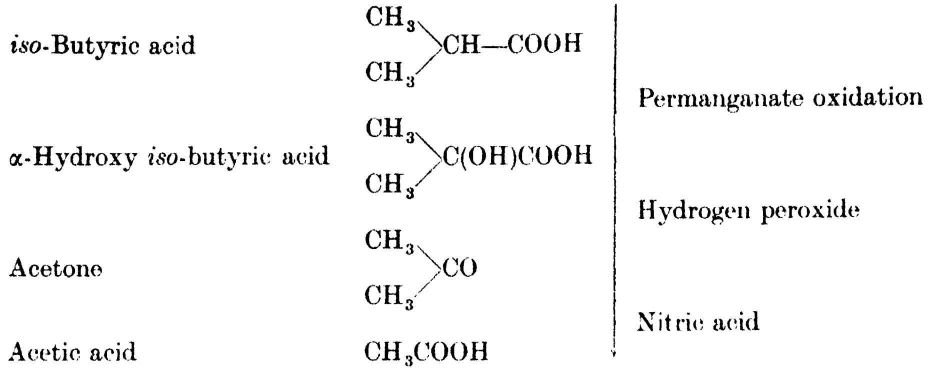
---

[1] Bost, Thesis, Univ. Lyons, 1938.

[2] Sabatier and Maihle, *C.R.*, 1912, **154**, 563.

[3] Chevreul, " Recherches sur les corps gras ", 1823, Paris.

The oxidation of *iso*-butyric acid can lead to the following sequence of reactions :—



iso-Butyric acid $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}COOH$

α-Hydroxy *iso*-butyric acid $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>C(OH)COOH$

Acetone $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CO$

Acetic acid CH_3COOH

There are but few properties of the higher aliphatic acids that call for comment ; pelargonic acid, being solid at 12° commences the series of acids solid at ordinary temperatures ; among the valeric acids is found the first optically active aliphatic acid—*l*-methylbutane acid—which was resolved by fractional crystallisation of the *d*-brucine salts.

Most of the higher acids are produced by malonic or acetoacetic ester synthesis, details of which are given in Appendix II to this chapter. Some interesting individual methods of preparation not involving the active methylene group are given below :—

(1) Oenanthic acid (heptane-acid) (8) is obtained by the oxidation of the heptaldehyde produced in the destructive distillation of castor oil :—

$$CH_3(CH_2)_5CHO \longrightarrow CH_3(CH_2)_5COOH \qquad (8)$$

(2) Raper[1] has devised a neat way of obtaining octoic acid ; two molecules of aldol, in the presence of dilute potassium carbonate solution, condense, somewhat unexpectedly, to form a hydroxyoctenal which when oxidised to the

$$\left|\begin{array}{l} CH_3\,.\,CH(OH)\,.\,CH_2\,.\,CHO + CH_3\,.\,CH(OH)CH_2\,.\,CHO \\ CH_3\,.\,CH(OH)CH_2\,.\,CH{=}CH\,.\,CH(OH)\,.\,CH_2\,.\,CHO \\ CH_3\,.\,CH(OH)CH_2\,.\,CH{=}CH\,.\,CH(OH)CH_2\,.\,COOH \\ CH_3\,.\,CH_2\,.\,CH_2\,.\,CH_2\,.\,CH_2\,.\,CH_2\,.\,CH_2\,.\,COOH \end{array}\right.\downarrow$$

corresponding acid and reduced with hydriodic acid, yields *n*-octoic acid.

(3) Many acids of between 5 and 9 carbon atoms may be obtained by the oxidation of unsaturated acids of long chain. This affords a simple method of making pelargonic acid from oleic acid

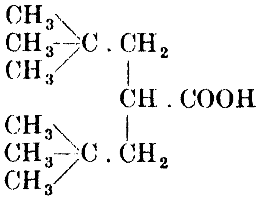
$$\begin{array}{l} CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH \\ CH_3(CH_2)_7COOH + HOOC(CH_2)_7COOH \end{array}$$

which at the same time yields azelaic acid. Clearly, an additional method of obtaining the long-chain saturated acids is by reduction of the unsaturated acid where this is readily available. An example is the formation of *n*-undecane acid, $CH_3(CH_2)_9COOH$, by reduction of the undecene acid obtained by the destructive distillation of castor oil.

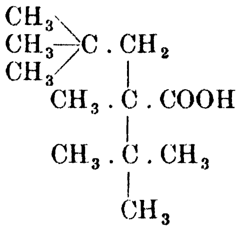
---

[1] Raper, *Trans. C.S.*, 1907, **91**, 1831.

(4) Arborescent acids, often known as 'Butlerow's acids' are obtained by the acid oxidation of tri-*iso*-butylene and similar unsaturated hydrocarbons. The two most commonly encountered are 2, 2, 4, 6, 6-penta-



(9)



(10)

methylheptane-4$_1$-acid (9) and 2, 2, 3, 3, 5, 5-hexamethylhexane-3$_1$ acid (10).

The higher fatty acids are nearly always prepared from their naturally occurring triglycerides. Thus, myristic acid is obtained from the glyceride, trimyristin, of nutmegs, and palmitic and stearic acids may be obtained from the naturally occurring stearin and palmitin. The chemistry of these fats is discussed in Appendix III to this chapter. It will be noted that the commonly occurring higher aliphatic acids are almost always those of even carbon number; the biochemical significance of this is discussed later, and is undoubtedly related to the building of fatty acids by a series of aldol condensations from two-carbon compounds. Biochemically, fats are also largely metabolised by the process of β-oxidation which leads to their degradation by two carbon atoms at each stage, the simple products, CH_3COCH_2COOH and CH_3COCH_3 being among the final stages; the diabetic is unable to utilise these substances which accumulate in the system. Attention has therefore been focussed on the aliphatic acids with an odd number of carbon atoms, which would by-pass these ketonic residues. A convenient acid was found in margaric acid, $C_{16}H_{33}COOH$, the tri-glyceride of which (margarin) has been used as a constituent of diet for diabetics under the name 'Intarvin'. The difficulty of obtaining adequate supplies militates against its more general use, as margaric acid is made by the cumbrous process of Krafft [1] in which calcium stearate and acetate are distilled together to give nonadecanone-2 which is oxidised by permanganate to margaric acid :—

$$\begin{array}{r|l} & CH_3 . (CH_2)_{16} . COOca + caOOCH_3 \\ \text{Heat} & \\ & CH_3 . (CH_2)_{16} . COCH_3 + CaCO_3 \\ \text{Oxidation} & \\ & \downarrow CH_3 . (CH_2)_{15} . COOH + CH_3COOH \end{array}$$

UNSATURATED ALIPHATIC ACIDS

Table VI shows the more common unsaturated acids with their formulæ and main physical properties. Of the various methods by which unsaturated acids can be prepared, some modification of Perkin's reaction is usually found to give good yields. In the simplest case Perkin's reaction involves the condensation of an aldehyde with the sodium salt of a carboxylic acid, in the presence of acetic anhydride. Presumably an aldol condensation followed by loss of water occurs :—

$$CH_3CHO + CH_3COONa \longrightarrow CH_3 . CH(OH)CH_2 . COONa$$
$$\longrightarrow CH_3 . CH{=}CH . COONa + H_2O$$

---

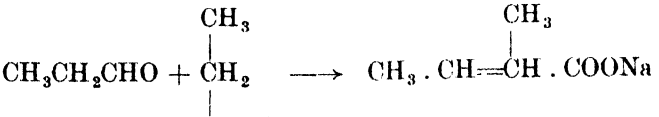
[1] Krafft, *Ber.*, 1879, **12**, 1672.

TABLE VI

Systematic name	Ordinary name	Formula	No. of double bonds	Position of double bonds	M.P.	B.P.	K × 10^5
Propene-2, acid	Acrylic acid	C_2H_3COOH	1	2	13°	142°	5·6
Butene-3, acid	Vinylacetic acid	C_3H_5COOH	1	3	−13°	71°/13 mm.	4·5
cis-Butene-2, acid	*iso*-Crotonic acid	C_3H_5COOH	1	2	16°	74°/15 mm.	4·0
trans-Butene-2, acid	Crotonic acid	C_3H_5COOH	1	2	77°	180°	2·4
2-Methylpropene-2, acid	Methylacrylic acid	C_3H_5COOH	1	2	16°	161°	—
Pentene-4, acid	Allylacetic acid	C_4H_7COOH	1	4	—	188°	—
Pentene-3, acid	Ethylidene propionic acid	C_4H_7COOH	1	3	+1°	90°/10 mm.	3·3
Pentene-2, acid	β-Ethylacrylic acid	C_4H_7COOH	1	2	—	92°/10 mm.	—
cis-Methylbutene-2, acid	Angelic acid	C_4H_7COOH	1	2	45°	185°	5·0
trans-Methylbutene-2, acid	Tiglic acid	C_4H_7COOH	1	2	64·5°	198°	0·9
2-Ethylpropene-2, acid	α-Ethylacrylic acid	C_4H_7COOH	1	2	−16°	83°/15 mm.	—
3-Methylbutene-2, acid	ββ-Dimethylacrylic acid	C_4H_7COOH	1	2	69°	194°	—
Hexene-5, acid	—	C_5H_9COOH	1	5	37°	107°/17 mm.	1·9
cis-Hexene-4, acid	—	C_5H_9COOH	1	4	13°	100°/10 mm.	1·7
trans-Hexene-4, acid	—	C_5H_9COOH	1	4	1°	111°/20 mm.	—
Hexene,-3 acid	Hydrosorbic acid	C_5H_9COOH	1	3	12°	107°/15 mm.	2·4
cis-Hexene-2, acid	—	C_5H_9COOH	1	2	—	202°	—
trans-Hexene-2, acid	Isohydrosorbic acid	C_5H_9COOH	1	2	33°	217°	1·9
4-Methylpentene-3, acid	Pyroterebic acid	C_5H_9COOH	1	3	—	104°/10 mm.	—
2, 2-Dimethylbutene-3, acid	Dimethylvinylacetic acid	C_5H_9COOH	1	2	71°	—	3·9
3, 4-Dimethylpentene-3, acid	Teracrylic acid	$C_6H_{11}COOH$	1	3	—	218°	—
2, 6-Dimethylheptene-5 acid	—	$C_8H_{15}COOH$	1	5	—	136°/13 mm.	—
Decene-1, acid-10	Decylenic acid	$C_9H_{17}COOH$	1	9	40°	142°/4 mm.	—
3, 7-Dimethyloctene-6, acid	Citronellic acid	$C_9H_{17}COOH$	1	6	—	143°/10 mm.	—
Undecene-10, acid	Undecylenic acid	$C_{10}H_{19}COOH$	1	10	24·5°	165°/15 mm.	—
Dodecene-4, acid	Linderic acid	$C_{11}H_{21}COOH$	1	4	1°	—	—
Dodecene-5, acid	Deuticetic acid	$C_{11}H_{21}COOH$	1	5	—	175°/15 mm.	—
Tetradecene-5, acid	Physeteric acid	$C_{13}H_{25}COOH$	1	5	—	195°/15 mm.	—
cis-Octadecene-9, acid	Oleic acid	$C_{17}H_{33}COOH$	1	9	13-16°	223°/10 mm.	—
trans-Octadecene-9, acid	Elaidic acid	$C_{17}H_{33}COOH$	1	9	44°	225°/10 mm.	—
cis-Octadecene-6, acid	Petroselinic acid	$C_{17}H_{33}COOH$	1	6	34°	—	—
trans-Octadecene-6, acid	*iso*-Petroselinic acid	$C_{17}H_{33}COOH$	1	6	54°	—	—

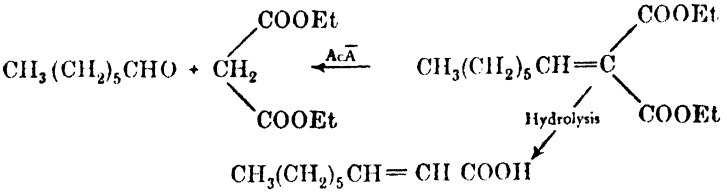
cis-Octadecene-11, acid	*cis*-Vaccenic acid	$C_{17}H_{33}COOH$	1	11	39·5°	196°/1·5 mm.	—
trans-Octadecene-11, acid	*trans*-Vaccenic acid	$C_{17}H_{33}COOH$	1	11	10°	196°/1·5 mm.	—
cis-Docosene-9, acid	Erucic acid	$C_{21}H_{41}COOH$	1	9	34°	255°/10 mm.	—
trans-Docosene-9, acid	Brassidic acid	$C_{21}H_{41}COOH$	1	9	65°	256°/10 mm.	—
cis-Tetracosene-15, acid	Selacholeic acid (Nevonic acid)	$C_{23}H_{45}COOH$	1	15	39°	—	—
trans-Tetracosene-15, acid		$C_{23}H_{45}COOH$	1	15	61°	—	—
Pentadiene-2, 4, acid	Vinylacrylic acid	C_4H_5COOH	2	2, 4	80°	polymerises	—
Hexadiene-2, 4, acid	Sorbic acid	C_5H_7COOH	2	2, 4	134·5°	—	—
3, 7-Dimethyloctadiene-2, 6, acid	Geranic acid	$C_9H_{15}COOH$	2	2, 6	—	153°/11 mm.	—
Octadecadiene-9, 12 acid	Linoleic acid	$C_{17}H_{31}COOH$	2	9, 12	24°	230°/15 mm.	—
3, 7-Dimethyloctatriene, 2, 4, 6, acid	Dehydrogeranic acid	$C_9H_{13}COOH$	3	2, 4, 6,	—	—	—
Hexadecatriene, 6, 10, 14, acid	Hiragonic acid	$C_{15}H_{25}COOH$	3	6, 10, 14	—	185°/15 mm.	—
Octadecatriene, 9, 11, 13, acid	Elæostearic acid	$C_{17}H_{29}COOH$	3	9, 11, 13	α, 14° β, 71°	—	—
Octadecatriene-9, 12, 15, acid	Linolenic acid	$C_{17}H_{29}COOH$	3	9, 12, 15	—	157°/2 mm.	—
Octadecatetraene-4, 8, 12, 15, acid	Moroctic acid	$C_{17}H_{27}COOH$	4	4, 8, 12, 15	—	—	—
Eicosatetrene-4, 8, 12, 16 acid	—	$C_{19}H_{31}COOH$	4	4, 8, 12, 16	—	—	—
Docosapentene-4, 8, 12, 15, 19, acid	Clupanodonic acid	$C_{21}H_{33}COOH$	5	4, 8, 12, 15, 19	—	—	—
Eicosatetrene, 5, 8, 11, 14 acid	Arachidonic acid	$C_{19}H_{31}COOH$	4	5, 8, 11, 14	—	—	—
				Triple bonds			
Propyne-2, acid	Propiolic acid	$C_2H\,.\,COOH$	1	2	9°	144° (decomp)	
Butyne-2, acid	Tetrolic acid	C_3H_3COOH	1	2	77°	99°/18 mm.	250
Pentyne-2, acid	—	C_4H_5COOH	1	2	50°	—	—
Hexyne-2, acid	—	C_5H_7COOH	1	2	27°	120°/16 mm.	—
Heptyne-2, acid	—	C_6H_9COOH	1	2	—	141°/14 mm.	—
Octyne-2, acid	—	$C_7H_{11}COOH$	1	2	5°	148°/19 mm.	—
Undecyne-10, acid	Dehydroundecylenic acid	$C_{10}H_{17}COOH$	1	10	43°	175°/15 mm.	—
Octadecyne-6, acid	Tariric acid	$C_{17}H_{31}COOH$	1	6	51°	—	—
Octadecyne-9, acid	Stearolic acid	$C_{17}H_{31}COOH$	1	9	48°	—	—
Docosyne-13, acid	—	$C_{21}H_{39}COOH$	1	13	57°	—	—
4-Methylhexadi-yne-1, 6, acid 4_1	Diallylenyl acetic	C_7H_7COOH	2	1, 6	47°	—	—

The process is most useful for obtaining the α-unsaturated acids, since it is in this position that the condensation normally takes place; thus, with propionaldehyde and sodium propionate, a branched chain acid (11) is obtained. An interesting variant is the corresponding condensation with malonic ester, yielding an unsaturated substituted malonic ester which yields an α-unsaturated aliphatic acid on hydrolysis. This method can be extended to give the aliphatic saturated acid by reduction.



$$CH_3CH_2CHO + \underset{\displaystyle COONa}{\overset{\displaystyle CH_3}{CH_2}} \longrightarrow CH_3 . CH{=}\overset{\displaystyle CH_3}{C} . COONa$$

(11)



Other methods for the production of the ethylenic acids include the oxidation of the corresponding aldehyde, e.g., acrolein → acrylic acid. The most widely used reagent in this reaction is silver oxide, which avoids the complications of more active reagents, which may attack the double bond. Naturally, the elimination of hydrogen bromide from a bromo acid by alcoholic potash may be used, but the yield is not always good.

$$CH_3 . CH_2 . CH_2 . CHBr . COOH \xrightarrow{KOH} CH_3 . CH_2 . CH{=}CH . COOH$$

In a similar manner the unsaturated bromides can be converted to the nitriles and to the corresponding acids quite easily :—

$$CH_3 . CH{=}CH . CH_2 . Br \longrightarrow CH_3 . CH{=}CH . CH_2CN \longrightarrow CH_3 . CH{=}CH . CH_2 . COOH$$

Often, when these steps are attempted either an alteration in position of, or an addition to, the double-bond is encountered. This may be avoided by using the corresponding di-bromide, which after the introduction of the carboxylic group, can be reconverted to the unsaturated compound by the method of Finkelstein.[1] The dibromo acid is treated with sodium iodide in acetone solution when the di-iodo compound is produced but decomposes into iodine and the unsaturated acid :—

$$CH_3 . CH{=}CH . CH_2OH \xrightarrow{Br_2} CH_3 . CHBr . CHBr . CH_2OH$$
$$\xrightarrow{\text{oxidn.}} CH_3 . CHBr . CHBr . COOH \xrightarrow[\text{acetone}]{\text{NaI in}} (CH_3 . CHI . CHI . COOH)$$
$$\longrightarrow CH_3CH{=}CH . COOH + I_2.$$

Acrylic acid, $CH_2{=}CH . COOH$, was first the subject of experiments by Redtenbacher[2] who obtained it in his researches on acrolein. It is best prepared by catalytic oxidation of acrolein, which is easily obtainable.

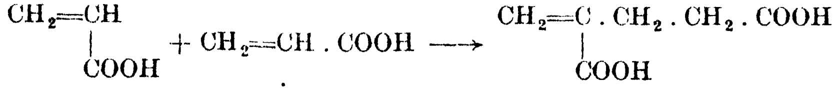
Like the majority of unsaturated functional compounds both the unsaturated group and the functional group are active. Thus, acrylic acid is a stronger acid than the corresponding saturated acid, propionic acid, and at the same time it is particularly reactive in respect of its unsaturated link, giving polymers which although not of themselves valuable, have analogues in the methylacrylic ester polymers which are of paramount importance in the transparent plastics field.

---

[1] Finkelstein, *Ber.*, 1910, **43**, 1530.

[2] Redtenbacher, *Ann.*, 1843, **47**, 113.

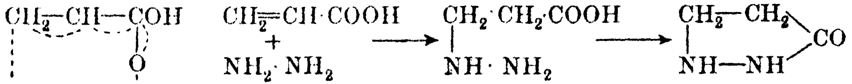
In the presence of sodium ethoxide a crystalline dimer is formed, 2 methyl-pentene-1, di-acid 2_1, 5 (12)



$$\underset{\text{COOH}}{\underset{|}{CH_2{=}CH}} + CH_2{=}CH.COOH \longrightarrow \underset{\text{COOH}}{\underset{|}{CH_2{=}C}}.CH_2.CH_2.COOH$$

(12)

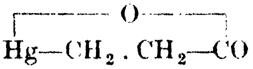
The usual additive reactions associated with the double bond are shown by acrylic acid, which is very easily reduced, even by sodium amalgam ; on the other hand, Markownikov's rule is not obeyed, even in circumstances where no diverting influence is present ; and halogen acids add to acrylic acid giving the β-halogeno-propionic acids. This is probably due to the conjugation of the carbonyl of the acid group with the double bond as in (13)



(13) (14)

leading to β-halogen addition. The addition of hydrazine leads first to the β-hydrazino-propionic acid which readily cyclises to pyrazolidone[1] (14).

Acrylic acid is characterised[2] by its difficultly soluble mercury salt, which decomposes with great readiness to give an anhydride of mercuripropionic acid (15). The decomposition of acrylic acid on caustic potash fusion yields potassium formate (16) and acetate. This fracture at the double bond is characteristic of the ethylenic acids with a ' 2 ' double bond. With acids in which the



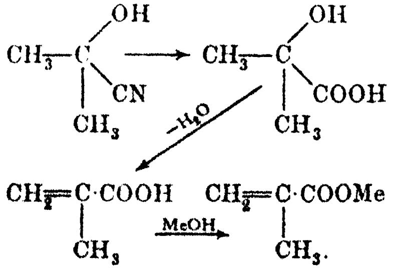
(15)

$$CH_2{=}CH.COOK \longrightarrow H.COOK + CH_3.COOK$$

(16)

double bond is at a position other than ' 2 ' no deductions can be drawn from the products of caustic fusion, since the bond is frequently displaced towards the carboxyl during the process.

α-*Methylacrylic acid*, which occurs free in the oil of Roman Chamomile was first prepared by Frankland and Duppa[3] from its ester, which they obtained by the dehydration of α-hydroxybutyric acid. In general, the properties of α-methylacrylic acid are similar to those of acrylic acid ; its methyl ester gives polymers of the utmost importance in the plastics industry as they are transparent and have a light transmissibility which is greater than that of glass. Enormous quantities of methyl methylacrylate are prepared industrially for the production of these plastics, by the treatment of acetone cyanhydrin with sulphuric acid at 110–120° followed by esterification :—



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[1] Rothenburg, *J. Pr. Chem.*, 1895, 2, **51**, 72.

[2] Bilman, *Ber.*, 1902, **35**, 2574.

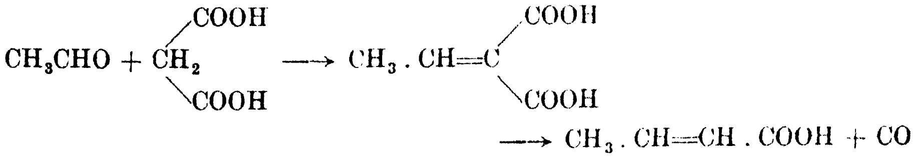
[3] Frankland and Duppa, *Ann.*, 1865, **136**, 12.

The polymerised methyl methylacrylate is encountered as a powder, 'diakon', which may be injection-moulded to give clear plastic articles, such as lenses.

The crotonic acids owe their name to the isolation of an acid by Schlippe,[1] in 1858, from croton seeds. Various methods analogous to those described for acrylic acid are available for preparing crotonic acid, which is, however, made in industrial quantities from acetaldehyde by processes involving the use of acetylene, sulphuric acid and water. Combination takes place, the crotonalde-

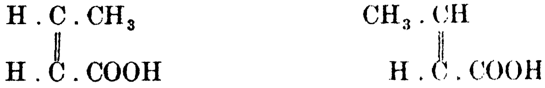
$$2C_2H_2 + H_2O \longrightarrow CH_3CH{=}CH \,.\, CHO$$

hyde constituting a by-product, or a main product according to the conditions of the reaction. The crotonaldehyde is oxidised catalytically to crotonic acid. Laboratory synthesis is best carried out [2] by condensing freshly distilled aldehyde with malonic acid in pyridine solution ; on raising the temperature carbon dioxide is eliminated from the condensation product and crotonic acid is formed :—



$$CH_3CHO + CH_2\begin{array}{l}\diagup COOH\\ \diagdown COOH\end{array} \longrightarrow CH_3\,.\,CH{=}C\begin{array}{l}\diagup COOH\\ \diagdown COOH\end{array}$$
$$\longrightarrow CH_3\,.\,CH{=}CH\,.\,COOH + CO_2$$

The assignment of the structures below, to crotonic and *iso*-crotonic acids, rests



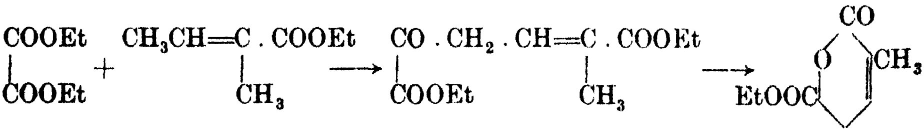
$$\begin{array}{c} H\,.\,C\,.\,CH_3\\ \|\\ H\,.\,C\,.\,COOH\end{array} \qquad\qquad \begin{array}{c} CH_3\,.\,CH\\ \|\\ H\,.\,C\,.\,COOH\end{array}$$

cis- or *iso*-crotonic acid

trans- or crotonic acid

partly on the fact that the physical properties are consistent with this arrangement (e.g., the *trans*- acid is usually the stronger acid) and partly on the nature of the optical activity of the products obtained by oxidation ; such data is unreliable, owing to the possibilities of *trans*-addition.

In its chemical reactions crotonic acid differs little from acrylic acid, save that the hydrogens of the methyl group are more labile and condense readily with aldehydes and ketonic esters. This is particularly true of α-methyl-



(17) (18)

crotonic ester which condenses with ethyl oxalate, to give a dicarboxylic ester (17) ; this loses water on treatment with hydrochloric acid to give the α-pyrone (18).

Iso-crotonic acid is comparatively difficult to obtain ; the method used by its discoverer in 1871, Geuther, is probably as good as any discovered since, and involves the reduction of α-chlorocrotonic acid with sodium amalgam. Crotonic, *iso*-crotonic and tetrolic acids are produced as the sodium salts, but the sodium *iso*-crotonate differs from the other in being readily soluble in cold alcohol ; thus a separation can be effected and the sodium salt converted to its acid.

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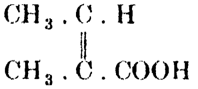
[1] Schlippe, *Ann.*, 1858, **106**, 24.

[2] Scheibler and Magasanik, *Ber.*, 1915, **48**, 1814 ; Auwers, *Ann.*, 1923, **432**, 46.

There is a strong tendency for *iso*-crotonic acid to pass over into crotonic acid; at 100° this is marked and the acid can only be purified by distillation in vacuum. Iodine, sunlight and ultra-violet light catalyse the reaction; a few minutes' exposure of aqueous solutions of *iso*-crotonic acid completes the transformation to crotonic acid.

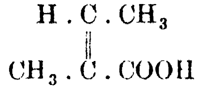
Of the unsaturated acids with five carbon atoms, angelic and tiglic acids are most widely distributed naturally; in addition, 3-methylbutene-2, acid is found in certain species of *Senecio*.

Angelic acid was discovered by Buchner[1] in angelica root; it has since been found in a variety of plants—sumbul root, and oil of cumin (Roman chamomile) from which the acid has been obtained for experimental purposes. It is a beautifully crystalline substance, not easily soluble in cold water, and has an aromatic odour. Tiglic acid is formed when angelic acid is irradiated with ultra-violet light or allowed to stand in the presence of a trace of bromine. Tiglic acid was obtained synthetically by Frankland and Duppa[2] before it was isolated from croton oil (Croton = *Croton Tiglium*) by Geuther and Fröhlich.[3] The two formulæ below indicate the difficulty of using the '*cis*' and '*trans*' denomination to describe the structure of any but the simplest substances.



$$\begin{array}{c} CH_3\,.\,C\,.\,H \\ \| \\ CH_3\,.\,C\,.\,COOH \end{array}$$

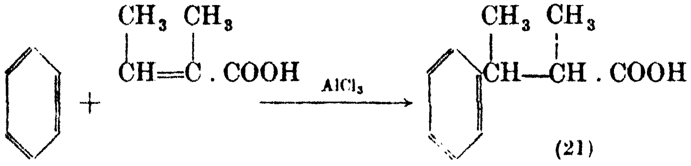
(19)



$$\begin{array}{c} H\,.\,C\,.\,CH_3 \\ \| \\ CH_3\,.\,C\,.\,COOH \end{array}$$

(20)

It will be observed that angelic acid (19) and tiglic acid (20) cannot be classified as '*cis*' and '*trans*' without specifying the groups to which these prefixes are referrable. In this case the angelic acid appears to be the unstable form and whilst angelic acid can be converted to tiglic acid, no reversal can be attained. The two acids may be formed simultaneously from α-hydroxy-α-methylbutyric acid by the following procedure. Methylethylketone is treated with sodium cyanide when the nitrile is formed: this is hydrolysed to the acid which on treatment with sulphuric acid loses the elements of water giving angelic and tiglic acids in proportion of approximately two of the former to one of the latter. As with other unsaturated acids, tiglic acid condenses with benzene in the presence of anhydrous aluminium chloride giving a dimethyl hydrocinnamic acid (21)



(21)

The Higher Olefinic Acids

A large number of unsaturated acids containing a single double bond and with six or more carbon atoms is known—some are listed in Table VII.

Of the acids containing six carbon atoms, hydrosorbic acid (24) is the one most commonly met with. It may be prepared by the reduction of the corresponding alcohol, which is found in Japanese peppermint oil, or by the condensation of

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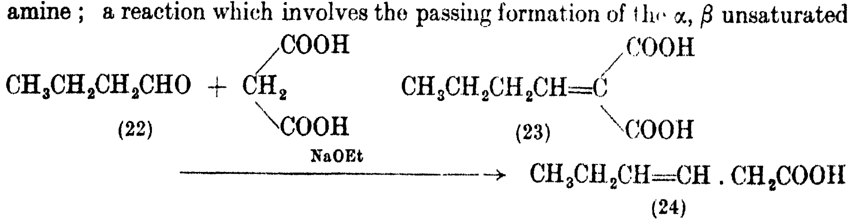
[1] Buchner, *Ann.*, 1854, **92**, 226.
[2] Frankland and Duppa, *ibid.*, 1865, **136**, 9.
[3] Geuther and Fröhlich, *Zeit. Chem.*, 1870, 459.

TABLE VII

UNSATURATED ACIDS FROM C_6–C_{11} (ONE DOUBLE BOND)

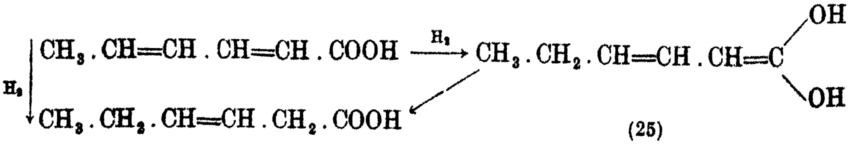
No. of carbons	Name	Formula	M.P.	B.P.
6	Hexene-2, acid	$CH_3CH_2CH_2CH{=}CH.COOH$ {*cis-* *trans-*	— 33°	202° 217°
6	Hexene-3, acid	$CH_3CH_2CH{=}CHCH_2COOH$	12°	107°/15 mm.
6	Hexene-4, acid (α form)	$CH_3CH{=}CH.CH_2CH_2COOH$ } ? cis- trans-	13°	100°/10 mm.
6	Hexene-4, acid (β-form)	$CH_3CH{=}CH.CH_2CH_2COOH$	1°	112°/20 mm.
6	Hexene-5, acid	$CH_2{=}CH.CH_2CH_2CH_2COOH$	37°	107°/17 mm.
6	2-Methylpentene-2, acid	$CH_3.CH_2CH{=}C(CH_3)COOH$	23°	112°/12 mm.
6	2-Methylpentene-3, acid	$CH_3CH{=}CH.CH(CH_3)COOH$	—	200°/745 mm.
6	3-Methylpentene-2, acid	$CH_3.CH_2C(CH_3){=}CH.COOH$ {*cis-* *trans-*	12° 49°	— 122°/22 mm.
6	3-Methylpentene-3, acid	$CH_3CH{=}C(CH_3)CH_2COOH$ {*cis-* *trans-*	1° 35°	— —
6	4-Methylpentene-2, acid	$CH_3CH(CH_3)CH{=}CH.COOH$	·	104°/10 mm.
6	4-Methylpentene-3, acid	$CH_3C(CH_3){=}CH.CH_2.COOH$	—	99°/10 mm.
7	Heptene-2, acid	$CH_3CH_2CH_2CH_2CH{=}CH.COOH$	—	228°
7	Heptene-3, acid	$CH_3CH_2CH_2CH{=}CH.CH_2COOH$	—	228°
7	Heptene-5, acid	$CH_3CH{=}CHCH_2CH_2CH_2COOH$	—	117°/11 mm.
7	Heptene-6, acid	$CH_2{=}CH.CH_2CH_2CH_2CH_2COOH$	—	226°
7	2-Methylhexene-2, acid	$CH_3.CH_2.CH_2.CH{=}C(CH_3)COOH$	34°	118°/11 mm.
7	2-Methylhexene-3, acid	$CH_3.CH_2.CH{=}CH.CH(CH_3)COOH$	—	124°/22 mm.
7	3-Methylhexene-2, acid	$CH_3.CH_2.CH_2C(CH_3){=}CH.COOH$	—	222·5°
7	4-Methylhexene-3, acid	$CH_3.CH_2C(CH_3){=}CH.CH_2.COOH$	121°	—
8	Octene-2, acid	$CH_3(CH_2)_4CH{=}CH.COOH$ {*cis-* *trans-*	— + 5°	127°/15 mm. 143°/15 mm.
8	6-Methylheptene-3, acid	$(CH_3)_2CH.CH_2.CH{=}CH.CH_2.COOH$	—	231-232°
8	6-Methylheptene-2, acid	$(CH_3)_2CH.CH_2.CH_2.CH{=}CH.COOH$	16·5°	227-228°
8	3, 5-Dimethylhexene-3, acid	$(CH_3)_2CH.CH{=}C(CH_3)CH_2COOH$	—	120°/4 mm.
9	Nonene-2, acid	$CH_3(CH_2)_5CH{=}CH.COOH$ {*cis-* *trans-*	— 2°	140°/15 mm. 154°/15 mm.
9	Nonene-8, acid	$CH_2{=}CH.(CH_2)_6COOH$	—	160°/15 mm.
9	3-Methyloctene-6, acid	$CH_3.CH{=}CH.CH_2.CH_2CH(CH_3)CH_2COOH$	—	145°/18 mm.
9	2, 6-Dimethylheptene-5, acid	$(CH_3)_2C{=}CH.CH_2.CH_2.CH(CH_3)COOH$	—	136°/13 mm.
10	Decene-4, acid	$CH_3(CH_2)_4CH{=}CH(CH_2)_2COOH$	—	154°/18 mm.
10	Decene-1, acid-10	$CH_2{=}CH(CH_2)_7COOH$	40°	142°/4 mm.
10	3-Methylnonene-2, acid	$CH_3(CH_2)_5.C(CH_3){=}CH.COOH$	—	158°/20 mm.
11	Undecene-9, acid	$CH_3CH{=}CH(CH_2)_7COOH$	11·4°	130°/1 mm.
11	Undecene-10, acid	$CH_2{=}CH(CH_2)_8COOH$	24·5°	165°/15 mm.

n-butyraldehyde (22) with malonic acid in the presence of a trace of triethanolamine ; a reaction which involves the passing formation of the α, β unsaturated



$$\underset{(22)}{CH_3CH_2CH_2CHO} + CH_2\begin{cases}COOH\\COOH\end{cases} \qquad \underset{(23)}{CH_3CH_2CH_2CH{=}C}\begin{cases}COOH\\COOH\end{cases} \xrightarrow{NaOEt} \underset{(24)}{CH_3CH_2CH{=}CH.CH_2COOH}$$

acid (23), which during the decarboxylation in presence of alkali yields hydrosorbic acid. Hydrosorbic acid, as its name implies, can be made by the regulated reduction of sorbic acid :—

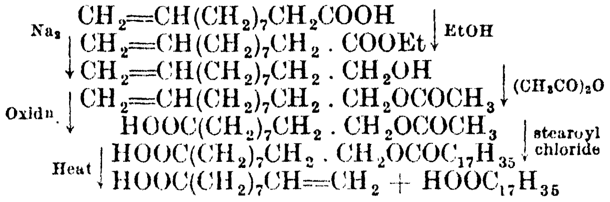


$$CH_3.CH{=}CH.CH{=}CH.COOH \xrightarrow{H_2} \underset{(25)}{CH_3.CH_2.CH{=}CH.CH{=}C}\begin{cases}OH\\OH\end{cases}$$

$$CH_3.CH{=}CH.CH{=}CH.COOH \xrightarrow{H_2} CH_3.CH_2.CH{=}CH.CH_2.COOH$$

a process which constitutes an excellent example of 1, 4- addition, although some investigators prefer to regard it as a 1, 6-addition, giving the enol (25), which changes into the keto form.

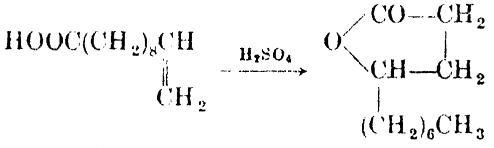
A normal decylenic acid (decene-1, acid-10) is found in butter and sperm oil as the glyceride. Industrially, decylenic acid is made from undecylenic acid (q.v.) by the following series of reactions :—



$$\begin{aligned}
&CH_2{=}CH(CH_2)_7CH_2COOH \\
&\downarrow \text{EtOH} \\
&CH_2{=}CH(CH_2)_7CH_2\,.\,COOEt \\
&\downarrow \text{Na}_2 \\
&CH_2{=}CH(CH_2)_7CH_2\,.\,CH_2OH \\
&\downarrow (CH_3CO)_2O \\
&CH_2{=}CH(CH_2)_7CH_2\,.\,CH_2OCOCH_3 \\
&\downarrow \text{Oxidn.} \\
&HOOC(CH_2)_7CH_2\,.\,CH_2OCOCH_3 \\
&\downarrow \text{stearoyl chloride} \\
&HOOC(CH_2)_7CH_2\,.\,CH_2OCOC_{17}H_{35} \\
&\downarrow \text{Heat} \\
&HOOC(CH_2)_7CH{=}CH_2 + HOOC_{17}H_{35}
\end{aligned}$$

The decene-1, acid-10 forms large crystals, m. 40°, with a characteristic, but not unpleasant odour.

Undecylenic acid (undecene-1, acid-11) (26) is a common article of commerce, being obtained by the destructive distillation of castor oil *in vacuo* ; œnanthol and a polyundecylenic acid are produced at the same time. It usually forms a solid crystalline mass, and is reduced to undecylic acid at ordinary temperatures by hydrogen in the presence of Raney nickel.[1] One of the more unusual reactions of undecylenic acid is its conversion by concentrated sulphuric acid at 30° to a γ-undecanolide (27), which is used in perfumery



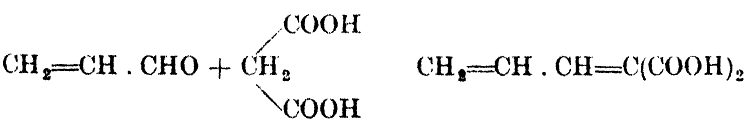
$$HOOC(CH_2)_8CH{=}CH_2 \xrightarrow{H_2SO_4} \gamma\text{-lactone: } O\text{—}CO\text{—}CH_2\text{—}CH_2\text{—}CH(O)\text{—}(CH_2)_6CH_3$$

(26) (27)

Of the higher unsaturated fatty acids containing a single double bond, some are of considerable importance as constituents of fish, animal and whale oils. A short list of these is given in Table VIII. The structures given are those commonly accepted, but the evidence on which some of these formulæ rests is slight, and further knowledge may necessitate revision of some of the double-bond positions.

Apart from such acids as geranic and rhodinic, which are discussed in the appropriate section of the chapter on terpenes, there are only one or two acids of the C_5—C_9 series carrying two or more double donds which are of importance.

Vinyl acrylic acid (pentadiene-2, 4, acid), $CH_2{=}CH\,.\,CH{=}CH\,.\,COOH$ is prepared largely by the condensation of acrolein and malonic acid in the presence of pyridine according to the method of Döbner [2] (28).



$$CH_2{=}CH\,.\,CHO + CH_2(COOH)_2 \qquad CH_2{=}CH\,.\,CH{=}C(COOH)_2 \longrightarrow CH_2{=}CH\,.\,CH{=}CHCOOH$$

(28) (29)

Vinylacrylic acid (29) is a most hygroscopic substance, forming large prismatic crystals, m. 80° and decomposing or polymerising at a higher temperature. On rapid heating of the barium salt Döbner obtained ethylbenzene and a hydrocarbon, C_8H_{12}, which he claimed was a tri*cyclo*öctane (30) ; this structure has not been confirmed.

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[1] Dupont, *Bull. Soc. Chim.*, 1936, 5, **3**, 1025.

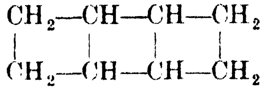
[2] Döbner, *Ber.*, 1902, **35**, 1137.

TABLE VIII

Naturally Occurring Higher Unsaturated Acids

No. of carbons	Natural source	Name	Structure	Properties
12	Lindera hypoglauca	Linderic acid	$CH_3(CH_2)CH{=}CH\,.\,CH_2\,.\,CH_2COOH$	m. 1° ; b. 165/170°, 12 mm.
12	Sperm oil	Denticetic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_2COOH$	,, b. 172-177°, 15 mm.
14	Cachalot oil	Physeteric acid	$CH_3(CH_2)_7CH{=}CH\,.\,(CH_2)_2COOH$	,, b. 192-197°, 15 mm.
14	Tretadenia	Tsuzuic acid	$CH_3(CH_2)_8CH{=}CH(CH_2)_2COOH$	
16	Arachis oil	Hypogeic acid	*cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_5COOH$	m. 33° ; b. 236/16 mm.
		Gaidic acid	*trans*-	
16	Oil from head of Physeter macrocephalus	Physetoleic acid identical with	$CH_3(CH_2)_5\,.\,CH{=}CH(CH_2)_7COOH$	,, ,,
16	Whale oil	Zoomaric acid		
18	Olives	Oleic acid	*cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	m. 13-16° ; b. 233°/10 mm.
18	Beef fat ; seeds	Elaidic acid	*trans*-$CH_3(CH_3)_7CH{=}CH(CH_2)_7COOH$	m. 44° : b. 225°/10 mm.
18	Parsley seed	Petroselinic acid	*cis*- *trans* $CH_3(CH_2)_{10}CH{=}CH(CH_2)_4COOH$	m. 30° m. 54°
18	Beef fat	Vaccenic acid	*cis*- *trans*- $(CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$	m. 39·5° 10° 196°/1·5 mm.
20	Herring	Gadoleic acid	$CH_3(CH_2)_7CH{=}CH\,.\,(CH_2)_9COOH$	m. 53-54°
22	Crucifers generally, particularly mustard and rape	Erucic acid	*cis*- $CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOH$	m. 34° ; b. 255°/10 mm.
		Brassidic acid	*trans*-	m. 65° ; b. 256°/10 mm.
22	Fish and whale oils	Cetoleic acid	$CH_3(CH_2)_9CH{=}CH(CH_2)_9COOH$	
24	Halibut liver oil	Selacholeic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_{13}COOH$	*cis*- m. 39°
	Human brain	Nervonic acid		*trans*- m. 61°
18	Many vegetable oils, particularly flax or linseed Animal fats	Linoleic acid	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	m. 24° ; b. 230°/16 mm.
16	Fish oils	Hiragonic acid	$CH_3\,.\,CH{=}CH(CH_2)_2CH{=}CH(CH_2)_2CH{=}CH(CH_2)_4COOH$	,, b. 180, 190°/15 mm
18	Plants ; Rosaceæ, Curcubitaceæ and Euphorbiaceæ	Elæostearic acid	$CH_3(CH_2)_3CH{=}CH\,.\,CH{=}CH\,.\,CH{=}CH(CH_2)_7COOH$	m. 48° ; b. 235°/12 mm.
18	Linseed, soya, herring	Linolenic acid	$CH_3CH_2CH{=}CH\,.\,CH_2CH{=}CH\,.\,CH_2CH{=}CH—$	,, b. 155°/2 mm.
18	Fish oils	Moroctic acid	$CH_3CH_2CH{=}CH\,.\,CH_2CH{=}CH(CH_2)_2CH{=}CH—(CH_2)_2CH{=}CH(CH_2)_2COOH$	
20	Butter, lecithin, animal fat	Arachidonic acid	$CH_3(CH_2)_4CH{=}CH\,.\,CH_2CH{=}CHCH_2CH{=}CH—CH_2CH{=}CH(CH_2)_4COOH$	
20	Sardine oil	Eicosatetrenoic acid	$CH_3(CH_2)_2CH{=}CHCH_2CH{=}CH(CH_2)_2—CH{=}CH(CH_2)_2CH_2{=}CH(CH_2)_2COOH$	
22	Sardine oil	Clupanodonic acid	$CH_3CH_2CH{=}CH(CH_2)_2CH{=}CH\,.\,CH_2CH{=}CH—(CH_2)_2CH{=}CH(CH_2)_2CH{=}CH(CH_2)_2COOH$	

Sorbic acid (33), was discovered by Hofmann [1] in the so-called 'mountain ash oil', an oil which separates during the evaporation of the crude calcium malate liquor obtained by neutralising with lime the expressed juice of the unripe berries of the mountain ash. This oil warmed with a little sulphuric acid gave crystalline sorbic acid. Its synthesis may be effected by condensing monobromoacetic ester and crotonaldehyde (31) in the presence of zinc, when a hydroxy acid (32) is obtained ; this acid loses water on heating with a solution of baryta giving an excellent yield of sorbic acid (33). An alternative method is the condensation of crotonaldehyde with malonic acid (34).



$$\begin{array}{cccc} \mathrm{CH_2}\!-\!\!\!\!&\mathrm{CH}\!-\!\!\!\!&\mathrm{CH}\!-\!\!\!\!&\mathrm{CH_2} \\ | & | & | & | \\ \mathrm{CH_2}\!-\!\!\!\!&\mathrm{CH}\!-\!\!\!\!&\mathrm{CH}\!-\!\!\!\!&\mathrm{CH_2} \end{array}$$

(30)

$$\begin{array}{l|l} \text{(31)}\ \mathrm{CH_3 . CH{=}CH . CHO + CH_2Br . COOEt} & \mathrm{Zn} \\ \text{(32)}\ \mathrm{CH_3 . CH{=}CH . CH(OH)CH_2 . COOH} & -\mathrm{H_2O} \\ \text{(33)}\ \mathrm{CH_3 . CH{=}CH . CH{=}CH . COOH} & \downarrow \end{array}$$

$$\begin{array}{l|l} \text{(34)}\ \mathrm{CH_3 . CH{=}CH . CHO + CH_2(COOH)_2} & \\ \quad\ \mathrm{CH_3 . CH{=}CH . CH{=}C(COOH)_2} & \mathrm{Py.} \\ \quad\ \mathrm{CH_3 . CH{=}CH . CH{=}CH . COOH} & \downarrow \end{array}$$

The Higher Unsaturated Acids

In many vegetable and fish oils, and to some extent in the fats of land animals, are a series of glycerides of the unsaturated fatty acids. Whilst in many vegetable oils such as olive and rape, these exist as the triglycerides of a single acid (e.g., olein) in animal fats it is usual to find only one of the three hydroxyl groups of glycerol esterified by an unsaturated acid, the other two being combined with a saturated radicle. The acids with more than one double bond, and their glycerides, are capable of absorbing oxygen from the air to form hard resinous materials ; oils containing such unsaturated bodies are termed 'drying' oils and their use in the manufacture of paints and varnishes is of paramount importance. The constitution of these unsaturated acids has been established by a number of researches, chief among which deals with the action of ozone upon the double bonds, and the nature of the products formed by the subsequent breakdown of the ozonides formed. Thus oleic acid forms an ozonide which breaks down to pelargonic aldehyde (35) and the half aldehyde of azelaic acid (36).

$$\mathrm{CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH} \Big\downarrow \text{ozonolysis}$$

$$\text{(35)}\ \mathrm{CH_3(CH_2)_7CHO} + \mathrm{CHO(CH_2)_7COOH}\ \text{(36)}$$

From such evidence it is easy to deduce that oleic acid has the structure of a octadecene-9, acid. In a similar way the structure of many simple unsaturated acids has been demonstrated, e.g., petroselinic acid yields the half aldehyde of adipic acid and dodecanal (37)

$$\mathrm{CH_3(CH_2)_{10}CH{=}CH(CH_2)_4COOH}$$

$$\text{(37)}\ \mathrm{CH_3(CH_2)_{10}CHO + CHO(CH_2)_4COOH.}$$

On the other hand the process is not so satisfactory in defining the structure of dien- or trien- acids where the double bonds are close together. This is well illustrated by the action of ozone and subsequent hydrolysis on linoleic acid. If linoleic acid be truly represented by (38) then the products of ozonolysis should be the malonic dialdehyde (40), the half aldehyde of azelaic acid (41) and valeraldehyde (39). In actual practice azelaic, butyric and glutaric acids are isolated. This is probably due to a shift of the second double bond during

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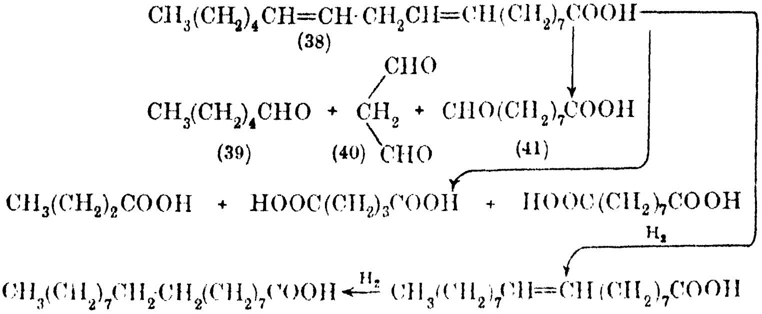
[1] Hofmann, *Ann.*, **1859**, **110**, 129.


$CH_3(CH_2)_4CH{=}CH{\cdot}CH_2CH{=}CH(CH_2)_7COOH$
(38)
$CH_3(CH_2)_4CHO$ + $CH_2(CHO)_2$ + $CHO(CH_2)_7COOH$
(39)
(40)
(41)
$CH_3(CH_2)_2COOH$ + $HOOC(CH_2)_3COOH$ + $HOOC(CH_2)_7COOH$
H_2
$CH_3(CH_2)_7CH_2CH_2(CH_2)_7COOH \xleftarrow{H_2} CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
(43)
(42)

the ozonolysis ; acceptance of the position of this bond at ' 12 ', is the result of careful observation of a large number of reactions. On catalytic reduction linoleic acid yields oleic acid (42) and finally stearic acid (43).

On the other hand with linolenic acid the normal products are obtained, enabling the structure to be deduced from this evidence with reasonable certainty (44) ; azelaic and malonic acids, together with propionaldehyde are formed

$$CH_3CH_2 . CH{=}CH . CH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$$
$$\downarrow$$
$$CH_3CH_2CHO + HOOCCH_2COOH + HOOCCH_2COOH + HOOC(CH_2)_7COOH$$

(44)

The biochemical importance of the higher unsaturated acids is difficult to over-estimate. It has been established that fish and animals are capable of building up ordinary fats (in which the acid stem is saturated) from carbohydrates, but that land animals are unable to build up in this way the specific unsaturated acids required for full nutrition. Evans and Burr[1] experimented with a diet employing sucrose as the sole source of carbohydrate (together with defatted casein, salts and vitamin supplements). Despite the ability which rats possess of synthesising saturated fats from carbohydrate they could not maintain life on the diet ; after some months they ceased to grow and developed definite signs of a deficiency syndrome. Their skin became affected, reproduction failed and they exhibited kidney derangement. This syndrome could be cured by the administration of small amounts of linseed oil or of linolenic or linoleic acids, but was *not* cured by the administration of saturated fats or of oleic acid.[2]

It follows from this and other data (*a*) that the higher unsaturated fatty acids occupy a proper place in the list of food accessory factors or vitamins, and (*b*) that they cannot be synthesised biologically and must be ingested. It is of great significance in these experiments that the three acids used :—

oleic acid : $CH_3CH_2CH_2CH_2CH_2CH_2CH_2 . CH_2 . CH{=}CH(CH_2)_7COOH$
linoleic acid : $CH_3CH_2CH_2CH_2CH_2CH{=}CH . CH_2 . CH{=}CH(CH_2)_7COOH$
linolenic acid : $CH_3CH_2CH{=}CHCH_2CH{=}CH . CH_2 . CH{=}CH(CH_2)_7COOH$

have an identical structure, save for the additional double bonds at ' 12 ' and ' 15 '. This is important, since it has been shown that the living animal can dehydrogenate stearic acid to oleic acid, by enzymic reduction at the 9–10 bond,[3] but it cannot embark on a second reduction giving an additional double bond at 12, 13. Turpeinen [1] prepared a dehydrostearic acid (octadecene-12, acid) from ricinoleic acid and found that it was equally ineffective in correcting the deficiency syndrome, which shows that it is not the position of the second double-bond which blocks the synthesis but the fact that no specific dehydrogenase exists in the animal system capable of introducing a *second* double bond when one already exists in the molecule.

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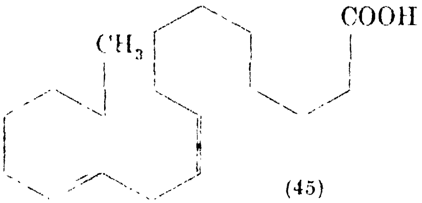
[1] Evans and Burr, *Proc. Soc. Exp. Biol. Med.*, 1927, **25**, 41.
[2] Burr, Burr and Miller, *J. Biol. Chem.*, 1932, **97**, 1.
[3] Lang and Addickes, *Z. Physiol. Chem.*, 1940, **262**, 123.

Linolenic acid is not widely distributed in the normal diet, but arachidonic and clupanodonic acids are well distributed in meat fat and fish oil and play a similar but more effective part in the correction of unsaturation deficiency syndromes, whilst Farmer and Heuvel [2] isolated from the molecular distillation a C_{22} acid with 6 double bonds (and an overpowering odour of cod liver) which had a great potency in correcting the growth stoppage of the syndrome, but was without action on the skin symptoms. The seat of the absorption and retention of the unsaturated fats appears to be the liver and the fat surrounding the adrenal cortex, which may signify some relation to the sterol family, as indicated by the rewritten formula (45) for linolenic acid. This is a particularly seductive speculation since there appears to be a biological link between unsaturated fatty acids, the fatty alcohols, the sterols and the hydrocarbon squalene. Some animals store up these products at one stage and others at another; indeed Tsujimoto [3] went so far as to suggest that the selachian group of fish should be classified according to the stage at which this storage took place in the liver, e.g.,



(45)

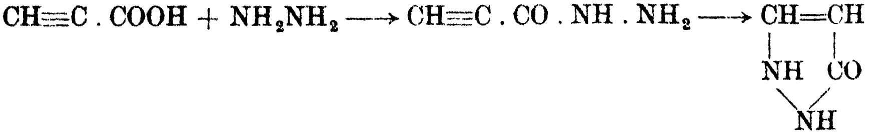
Class I.—All liver-fat as glycerides of fatty acids; only 1–2 per cent. unsaponifiable matter.

Class II.—Fish containing 10–14 per cent. of unsaponifiable matter in the liver-fat, mainly sterols + selachyl and chimyl alcohols.

Class III.—Fish whose liver-fat consists of batyl and selachyl alcohols with substantial amounts of squalene.

ACETYLENIC ACIDS

With the possible exception of tariric acid, $CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOH$, the acetylenic acids do not occur naturally. The simplest acid of the series, propiolic acid (propyne-2, acid), $CH{\equiv}C\,.\,COOH$, was first obtained by Bandrowski [4] (1880) by boiling acetylene dicarboxylic acid in aqueous solution. Propiolic acid resembles acetic acid very strongly; it melts at 9° C., boils about 140° and has a similar but more pungent odour. Chemically, it possesses all the attributes of an organic acid, giving esters, nitrile and amide. With hydrazine, however, it gives a pyrazolone:—



$$\mathrm{CH{\equiv}C\,.\,COOH + NH_2NH_2 \longrightarrow CH{\equiv}C\,.\,CO\,.\,NH\,.\,NH_2 \longrightarrow \begin{array}{c} CH{=}CH \\ |\qquad | \\ NH\quad CO \\ \diagdown\ \diagup \\ NH \end{array}}$$

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[1] Turpeinen, *J. Nutrition*, 1938, **15**, 351.

[2] Farmer and v. Heuvel, *J.S.C.I.*, 1938, **57**, 24.

[3] Tsujimoto, *ibid.*, 1932, **51**, 3171.

[4] Bandrowski, *Ber.*, 1880, **13**, 2340; 1882, **15**, 2701.

It retains, however, many of the properties of an acetylene, giving explosive salts—the potassium salt detonates at 105°—and the copper derivative which is a siskin-green powder, is particularly susceptible to shock. Propiolic acid polymerises on long standing to trimesic acid. The analogues of propiolic acid are seldom met with; some are described in Table IX.

TABLE IX

Acid	Formula	M.P.	B.P.
Propiolic acid	$H.C\equiv C.COOH$	9°	144°
Tetrolic acid	$CH_3.C\equiv C.COOH$	77°	99°/18 mm.
Hexyne-2-acid	$CH_3(CH_2)_2C\equiv C.COOH$	27°	120°/16 mm.
Heptyne-2-acid	$CH_3(CH_2)_3C\equiv C.COOH$	--	141°/24 mm.
Octyne-2-acid	$CH_3(CH_2)_4C\equiv C.COOH$	5°	148°/19 mm.
Undecyne-10-acid	$CH\equiv C(CH_2)_8COOH$	43°	175°/15 mm.
Palmitolic acid	$CH_3(CH_2)_7C\equiv C(CH_2)_5COOH$	47°	—
Stearolic acid	$CH_3(CH_2)_7C\equiv C(CH_2)_7COOH$	48°	---
Tariric acid	$CH_3(CH_2)_{10}C\equiv C(CH_2)_4COOH$	50·5°	---
Docosyne-13, acid	$CH_3(CH_2)_7C\equiv C(CH_2)_{11}COOH$	57°	---

The methyl ester of octyn-2-acid, is used extensively in perfumery for obtaining a fresh violet note. It is to be found in trade lists as 'methyl heptine carbonate' and is made from heptaldehyde which is readily available from the destructive distillation of castor oil. The formation of the acid, which is depicted in the formulæ below, is a typical example of the method used for the synthesis of the higher α-acetylenic acids:—

$$CH_3(CH_2)_4CH_2.CHO \xrightarrow{PCl_5} CH_3(CH_2)_4CH_2.CHCl_2 \xrightarrow{NaOH} CH_3(CH_2)_4C\equiv CH$$

$$\xrightarrow[CO_2]{NaNH_2} CH_3(CH_2)_4C\equiv C.COOH \xrightarrow{\text{esterification}} CH_3(CH_2)_4C\equiv C.COOMe$$

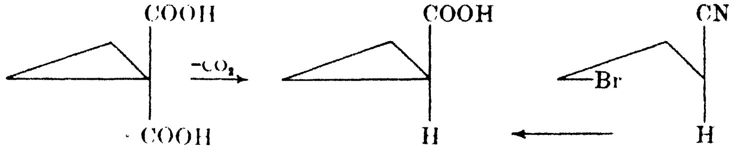
The corresponding 'methyl octine carbonate' is also used in the same capacity. Stearolic and palmitolic acids are made from the corresponding olefinic acids by addition of bromine to form the dibromo acid, followed by treatment with caustic soda effecting the removal of two molecular proportions of hydrobromic acid.

Tariric acid forms 20 per cent. of the tariri grain of Guatemala (*Picrammia* species). It is noteworthy that this acid is the triple-bond analogue of stearic acid, to which it may be reduced either catalytically or by phosphorus and iodine (46); sulphuric acid converts it to ketostearic acid (47).

$$\begin{tikzcd}
\underset{(46)}{CH_3(CH_2)_{10}C\equiv C(CH_2)_4COOH} \arrow[d, "H_2SO_4"'] \arrow[dr, "2H_2"] & \\
\underset{(47)}{CH_3(CH_2)_{10}CH_2.CO(CH_2)_4COOH} & CH_3(CH_2)_{16}COOH
\end{tikzcd}$$

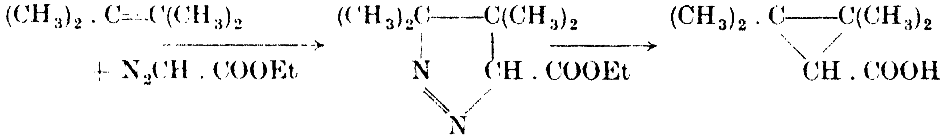
The Alicyclic Monocarboxylic Acids

The group is divided into two classes, those in which the carboxyl is attached directly to the ring, and those in which it forms part of a side-chain. Among the general methods for preparing members of the former group is the decarboxylation of 1, 1-dicarboxylic acids by heat. The dicarboxylic acids (see later) are almost invariably obtained by a malonic or cyanacetic ester synthesis and on heating a loss of carbon dioxide takes place leaving the monocarboxylic acid. Thus, *cyclo*propane 1, 1-dicarboxylic acid (48) on heating in an oil-bath is converted to the monocarboxylic acid (49), a substance with a sharp smell, m. 19°, and a general resemblance to acetic acid. An excellent alternative method for making this particular acid is the action of potash on γ-bromobutyronitrile (50) in which the loss of hydrobromic acid leads to a cyano*cyclo*propane which hydrolyses to the acid.

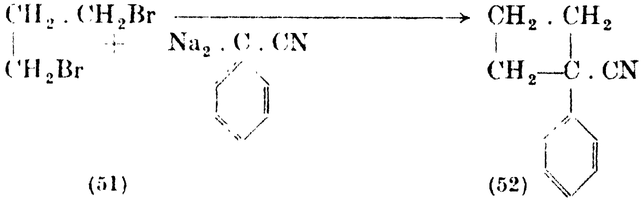


(48) (49) (50)

Derivatives of *cyclo*propane carboxylic acid are often made by the action of diazoacetic ester on the unsaturated hydrocarbon followed by heating the nitrogenous addition product, e.g.,



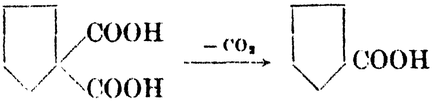
The simple *cyclo*-butane carboxylic acids are difficult to prepare and are little known; the method of Case[1] in which a 1, 3-dibromo compound is condensed with the disodium derivative of an α-cyano compound (e.g., benzyl cyanide) (51) is capable of giving a moderate yield of product (52), but succeeds better with aryl than alkyl compounds. The simple *cyclo*-butane carboxylic acid is singular in that whilst difficult of preparation it is stable when prepared, in fact, the ring is not opened by bromine, but is brominated, 1-bromo*cyclo*butane carboxylic acid being obtained.



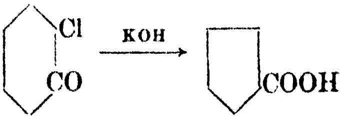
(51) (52)

*cyclo*Pentane carboxylic acid and its derivatives are more plentiful and better known than those of *cyclo*butane; the following methods serve for their preparation :—

(1) Loss of carbon dioxide from the 1, 1-dicarboxylic acids obtained by the malonic ester method :—



(2) The peculiar extrusion reaction which takes place when 2-chloro*cyclo*hexanone is warmed with alcoholic potash :—



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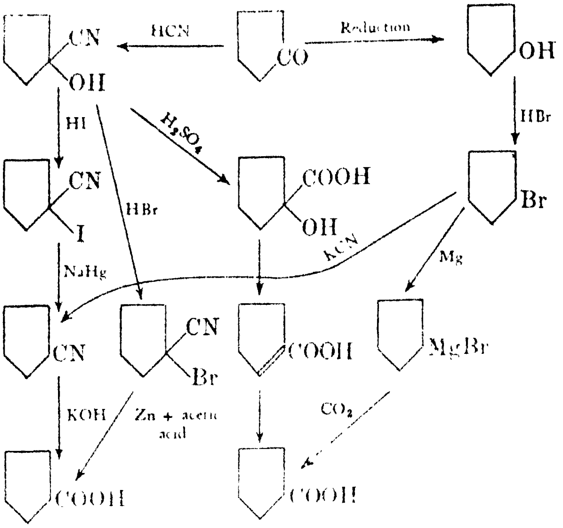
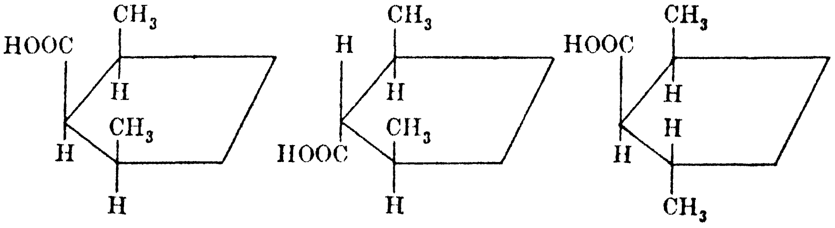
[1] Case, *J.A.C.S.*, 1934, **36**, 716.

(3) A group of methods commencing with *cyclo*pentanone. These are symbolised below :—



The simple alkyl derivatives are similarly prepared ; all the simple derivatives of *cyclo*pentane carboxylic acid have a repulsive sweat-like odour. As with the previously discussed members of the *cyclo*pentane group, there are numerous stereochemically possible forms, not all of which have been isolated. In the case, however, of the 2, 5-dimethyl*cyclo*pentane carboxylic acid the three geometrical isomers are known :—

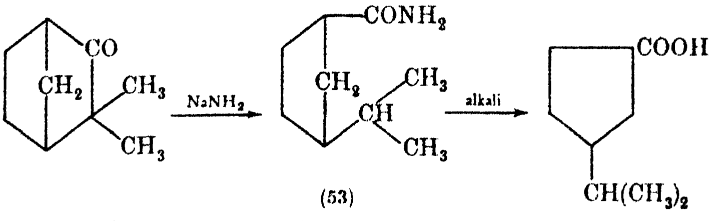


cis-I m. 26–30°

cis-II m. 75–77°

trans- m. 49–50

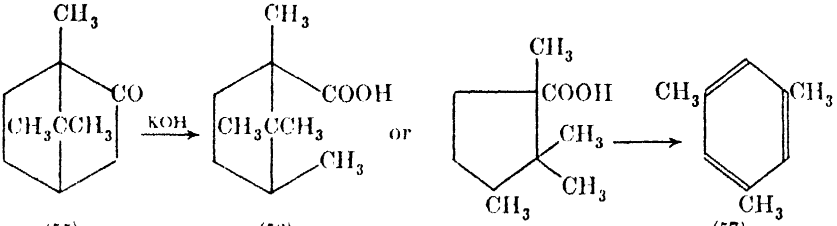
Many of the alkyl derivatives of this series are closely related to the bicyclic terpenes, as their names indicate. Table IX summarises the data concerning the more important members of the series. A large variety of methods has been used for obtaining the members of this series from the terpenes. Thus, Semmler's method is to treat a bicyclic terpene ketone with sodamide, e.g.,



(53) (54)

In this way the ring is opened at the keto group and the amide of the *cyclo*pentane acid is produced (53) ; this, with alkali, gives the acid itself (54). In some cases, as with camphor, the *cyclo*pentane derivative (56) is formed by

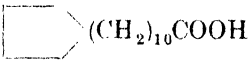
direct opening of the ring when the terpene is fused with potash[1] (55). The



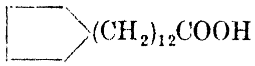
(55) (56) (57)

particular acid obtained in the last example, 1, 2, 2, 3-tetramethyl *cyclo*pentane carboxylic acid has the unusual property of being converted to hexahydromesitylene by heating with hydriodic acid under pressure.

The 11-*cyclo*pentylundecane acid (58) and 13-*cyclo*pentyltridecane acid (59) are important as the fully hydrogenated analogues of hydnocarpic and

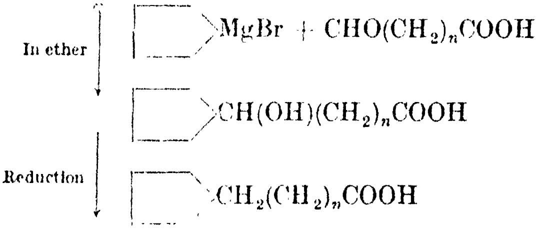


(58)



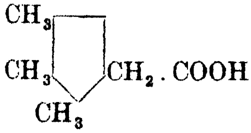
(59)

chaulmoogric acids, the esters of which have a considerable value in the treatment of leprosy. They were synthesised by Noller and Adams[2] by the following sequence of reactions :—

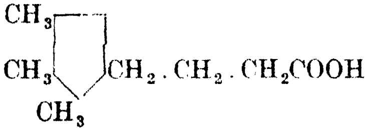


Thus, for dihydrohydnocarpic acid the half aldehyde of undecane diacid was condensed with *cyclo*pentyl magnesium bromide ; for dihydrochaulmoogric acid the half aldehyde of brassylic acid was used.

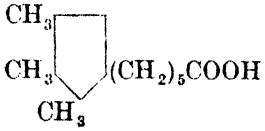
It may also be added that numerous acids, which are largely derived from the structures (60 to 62) are found in crude petroleum. They constitute the



(60)



(61)



(62)

so-called naphthenic acids and are substantially derivatives of the 2, 3, 4-trimethyl*cyclo*pentane alkane acids, although, of course, other nuclei are represented.

The *cyclo*hexane acids are the most numerous of the *cyclo*alkane acids ; among the alkyl derivatives there is considerable scope for geometrical isomerism, and whilst there are seven monomethyl derivatives of hexahydrobenzoic acid, there are thirty-two dimethyl derivatives.

The most readily accessible method of preparing many of the *cyclo*hexane carboxylic acids is by reduction of the corresponding benzene derivatives with sodium and amyl alcohol, or by catalytic reduction with hydrogen in the presence of Raney nickel. Practically, an excellent method of preparing the parent member of the series, hexahydrobenzoic acid, is to react *cyclo*hexyl magnesium bromide with carbon dioxide. In addition, malonic ester methods can be used with success.

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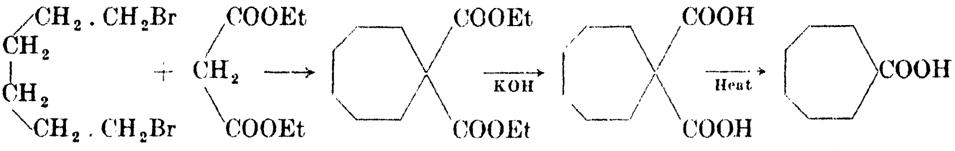
[1] Gueibet, *Bull. Soc. Chim.*, 1909, 4 5, 418 ; 1910, 4 7, 69.

[2] Noller and Adams, *J.A.C.S.*, 1926, 48, 1080.

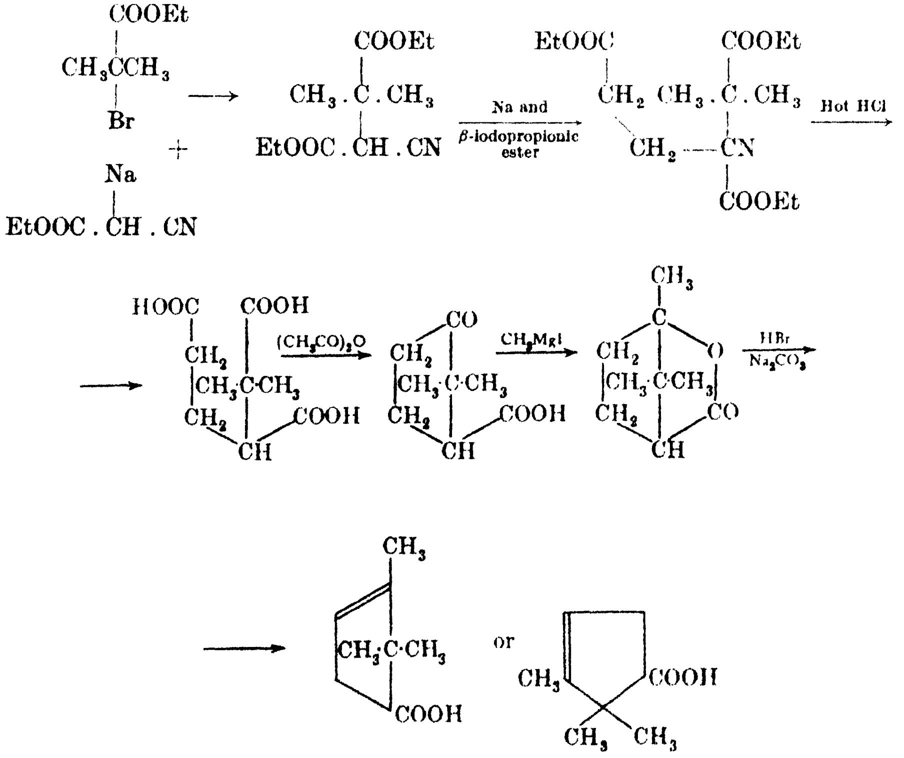
Surprisingly, *cyclo*heptane carboxylic acid occurs naturally in the oil of *Cyndus indicus*[1]; apart from this isolated instance, the *cyclo*heptane carboxylic acids are curiosities of the laboratory. Condensation of 1, 6-dibromohexane with malonic ester (63) yields the ester of *cyclo*heptane dicarboxylic acid (64) which yields the di-acid (65) and mono-acid (66) on hydrolysis and heating respectively.



(63) (64) (65) (66)

*Cyclo*Alkene Monocarboxylic Acids

Reference to Table X in which the main examples of the *cyclo*alkene carboxylic acids are summarised will show that there are no *cyclo*propene or cyclobutene acids; these are almost unknown, and whilst one or two highly substituted *cyclo*propene carboxylic esters have been prepared, no authenticated *cyclo*butene acids have been recorded. *Cyclo*Pentene acids are plentiful enough and a wide range of methods is available for preparing them by degradation of the appropriate bicyclic terpenes. Thus, α-campholytic acid has been prepared, not only from camphor but by the synthesis of Perkin and Thorpe.[2] The stages in this synthesis are outlined in the formulæ below :—



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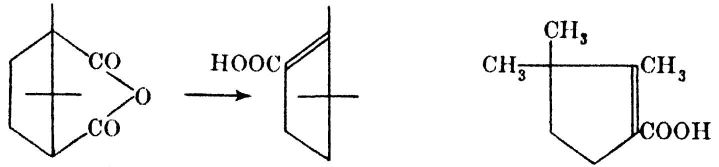
[1] Watson, *J.C.S.*, 1913, **103**, 550.

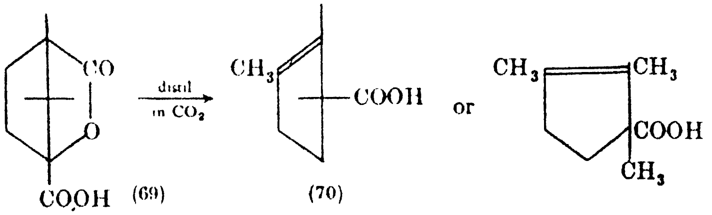
[2] Perkin and Thorpe, *J.C.S.*, 1904, **85**, 145; 1906, **89**, 799.

β-Campholytic acid (68) is readily obtained by the action of anhydrous aluminium chloride on camphoric anhydride (67) :—



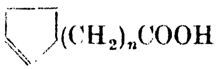
(67) (68)

whilst the isomeric laurolenic acid (70) is obtained by direct distillation of camphanic acid (69) in a current of carbon dioxide, from which it is clear that a deep-seated change has taken place during the transformation.

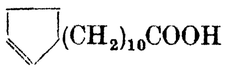


(69) (70)

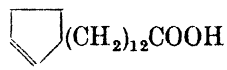
The complete series of *cyclo*pentenyl-2, alkane acids from $n = 1$ to $n = 14$. (71) is known. The unusual attention which has been accorded this group is



(71)



(72)



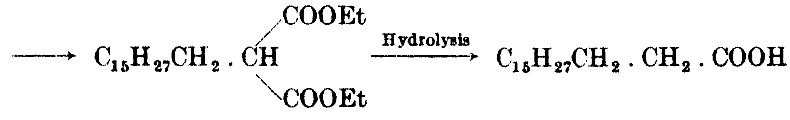
(73)

due to the fact that the two acids, hydnocarpic and chaulmoogric (72) and (73) are found as their esters in the oil of various species of *Hydnocarpus* and are of paramount value in the treatment of leprosy.

The structure of these two acids has been established by the following experiments :—

(1) Stanley and Adams[1] converted hydnocarpic to chaulmoogric acid by the following steps :—

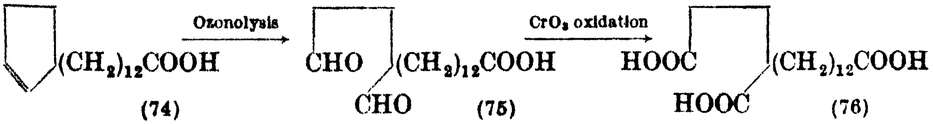
$$\underset{\text{Hydnocarpic acid}}{C_{15}H_{27}COOH} \xrightarrow[\text{alcohol}]{\text{Na}+} \underset{\text{Hydnocarpyl alcohol}}{C_{15}H_{27}CH_2OH} \xrightarrow{\text{HBr}} \underset{\text{Hydnocarpyl bromide}}{C_{15}H_{27}CH_2Br}$$



$$\longrightarrow \underset{\text{Hydnocarpyl-malonic ester}}{C_{15}H_{27}CH_2 . CH\begin{matrix}\diagup COOEt \\ \diagdown COOEt\end{matrix}} \xrightarrow{\text{Hydrolysis}} \underset{\text{Chaulmoogric acid}}{C_{15}H_{27}CH_2 . CH_2 . COOH}$$

The chaulmoogric acid so obtained is identical with that obtained from natural sources.

(2) When chaulmoogric acid is oxidised by ozone[2] a dialdehyde acid, 4-methyl heptadecane, 1, 4_1-dial-17 acid (75) is formed which was recognised by chromic oxidation to the corresponding tricarboxylic acid (76).



(74) (75) (76)

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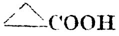
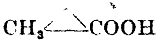
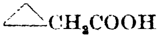
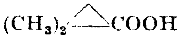
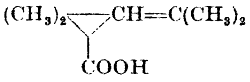
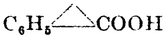
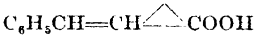
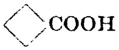
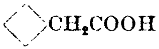
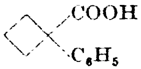
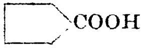
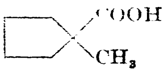
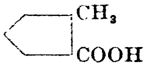
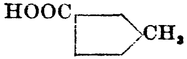
[1] Stanley and Adams, *J.A.C.S.*, 1929, **51**, 1515.
[2] Shriner and Adams, *ibid.*, 1925, **47**, 2727.

TABLE X

SOME *cyclo*ALKANE MONOCARBOXYLIC ACIDS

Name	Formula	Acid		Amide
		M.P.	B.P.	M.P.
***cyclo*Propane carboxylic acid**		19°	182°	124°
Methyl *cyclo*propane carboxylic acid		—	96°/14 mm.	—
***cyclo*Propylacetic acid**		—	190°	—
Dimethyl-*cyclo*propane carboxylic acid		—	115°/15 mm.	177°
2, 2 Dimethyl-3-butenyl*cyclo*propane carboxylic acid	 *cis*-	116°	—	101°
	trans-	—	143·6°/13 mm.	—
Phenyl*cyclo*propyl carboxylic acid		105°	—	188°
Styryl*cyclo*propyl carboxylic acid		130°	—	160°
***cyclo*Butyl carboxylic acid**		– 2°	196°	153°
***cyclo*Butyl acetic acid**		—	117°/17 mm.	179°
1-Phenyl-*cyclo*butyl carboxylic acid		107°	—	—
***cyclo*Pentane carboxylic acid**		4°	93°/7 mm.	179°
1-Methyl*cyclo*pentane carboxylic acid		—	117°/16 mm.	125°
2-Methyl*cyclo*pentane carboxylic acid	 natural	—	216°	123°
	synthetic	—	113°/13 mm.	147°
3-Methyl*cyclo*pentane carboxylic acid	 *d* and *l*	—	111°/13 mm.	150°

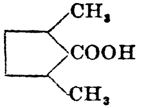
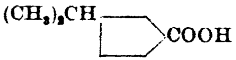
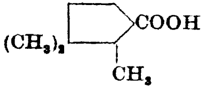
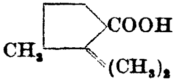
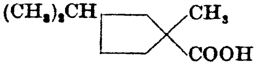
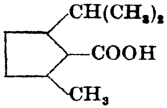
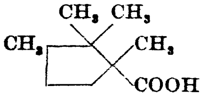
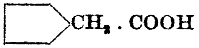
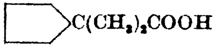
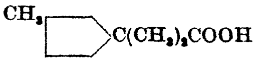
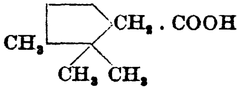
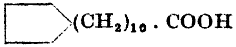
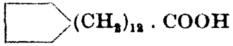
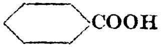
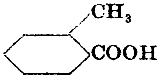
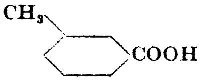
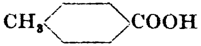
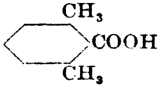
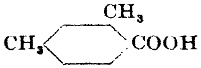
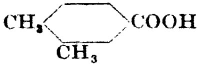
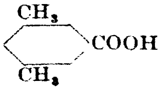
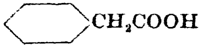
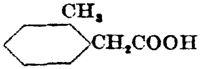
2, 5-Dimethyl*cyclo*pentane carboxylic acid		*cis-* I *cis-* II *trans-*	26-30° 75-77° 49-50°	— — —	— — —
3-*Iso*propyl*cyclo*pentane carboxylic acid			—	138°/12 mm.	167°
2, 3, 3-Trimethyl*cyclo*pentane carboxylic acid		Inactive Active	— —	135°/15 mm. 178°/10 mm.	165° 51°
2, 2, 3-Trimethyl*cyclo*pentane carboxylic acid		Inactive Active	— —	247° —	104° 87°
1-Methyl-3-*iso*-propyl*cyclo*pentane carboxylic acid **Fencholic acid**		Inactive Active	— 18-19°	— 140-141°/10 mm.	116° —
2-Methyl-5-*iso*-propyl*cyclo*pentane carboxylic acid **Dihydropulegenic acid**			— 18°	138°/11 mm.	151°
1, 2, 2, 3-Tetramethyl*cyclo*pentane carboxylic acid **Campholic acid**			109°	—	90°
***cyclo*Pentyl acetic acid**			14°	134°/23 mm.	145°
***cyclo*Pentyl*iso*butyric acid**			—	—	142°
3-Methyl*cyclo*pentyl*iso*butyric acid **(Dihydrofencholenic acid)**			—	260°	135°
2, 2, 3-Trimethyl*cyclo*pentyl acetic acid **(Dihydrocampholenic acid)**		Active Inactive *cis-* Inactive *trans-*	— —	160°/22 mm. 160°/22 mm.	143° 125°

TABLE X—(*Continued*)

Name	Formula		Acid		Amide
			M.P.	B.P.	M.P.
Dihydrohydnocarpic acid			63°	—	115°
Dihydrochaulmoogric acid			71°	248°/20 mm.	106°
Hexahydrobenzoic			30°	115·7°/13 mm.	186°
Hexahydro-*o*-toluic acid		*cis-*	—	123°/10 mm.	152°
		trans-	52°	125°/12 mm.	180°
Hexahydro-*m*-toluic acid		Inactive	—	245°	156°
		dextro-	—	133°/13 mm.	156°
Hexahydro-*p*-toluic acid		*cis-*	—	140°/20 mm.	178°
		trans-	113°	135°/16 mm.	221°
2, 6 Dimethylhexahydrobenzoic acid			75°	252°	—
2, 4-Dimethylhexahydrobenzoic acid		*cis-*	—	252°	142°
		trans-	77°	252°	190°
3, 4-Dimethylhexahydrobenzoic acid			—	251°	—
3, 5-Dimethylhexahydrobenzoic acid		α-	—	139°/15 mm.	—
		β-	66°	—	141°
***cyclo*-Hexylacetic acid**			32°	135°/13 mm.	172°
2-Methyl*cyclo*hexylacetic acid			—	—	161°

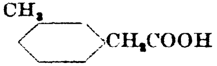
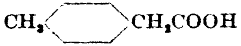
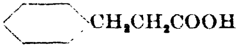
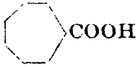
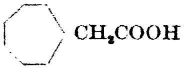
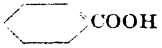
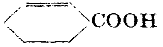
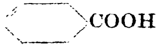
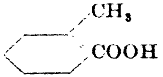
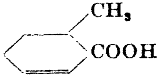
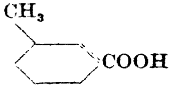
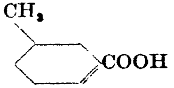
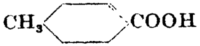
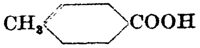
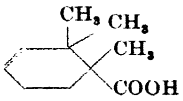
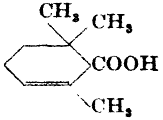
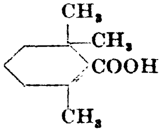
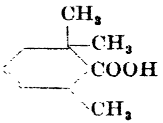
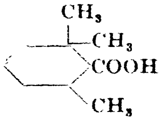
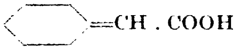
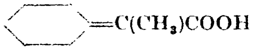
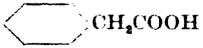
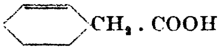
3-Methyl*cyclo*hexylacetic acid			—	152°/30 mm.	—
4-Methyl*cyclo*hexylacetic acid			74°	—	162°
β-*cyclo*Hexylpropionic acid			6°	268°	123°
***cyclo*Heptyl carboxylic acid**			—	139°/15 mm.	194°
***cyclo*Heptyl acetic acid**			—	165°/19 mm.	168°
***cyclo*-Hexene-1, carboxylic acid**			38°	134°/8 mm.	129°
***cyclo*-Hexene-2, carboxylic acid**			70°	120°/10 mm.	144°
***cyclo*-Hexene-3, carboxylic acid**			15°	236°	—
2-Methyl*cyclo*hexene-1, carboxylic acid			88°	—	—
2-Methyl*cyclo*hexene-5, carboxylic acid		*cis-* *trans-*	— 62°	146°/20 mm. 163°/30 mm.	— —
3-Methyl*cyclo*hexene-1, carboxylic acid			26°	—	—
3-Methyl*cyclo*hexene-6, carboxylic acid			155-160°	—	—
4-Methyl*cyclo*hexene-1, carboxylic acid			134°	—	—
4-Methyl*cyclo*hexene-3, carboxylic acid			99°	—	—

TABLE X—(*Continued*)

Name	Formula	Acid		Amide
		M.P.	B.P.	M.P.
Camphorenic acid		161°	—	—
α-*cyclo*Geranic acid		106°	—	—
β-*cyclo*Geranic acid		94°	—	—
Δ³-*cyclo*Geranic acid		76° 84°	— —	— —
Δ⁴-*cyclo*Geranic acid		102°	—	—
***cyclo*Hexylidene acetic acid**		91°	—	—
α-*cyclo*Hexylidene propionic acid		—	—	ethyl ester b. 109°/10 mm.
***cyclo*Hexenyl-1, acetic acid**		38°	145°/17 mm.	—
***cyclo*Hexenyl-2, acetic acid**		12°	120°/17 mm.	—

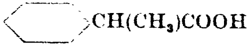
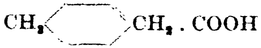
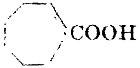
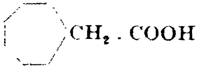
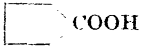
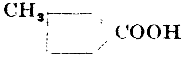
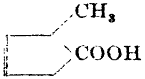
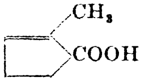
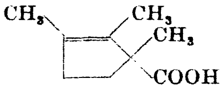
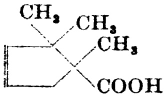
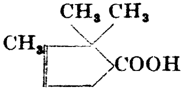
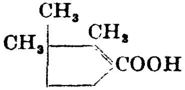
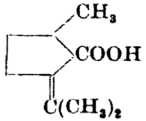
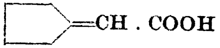
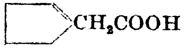
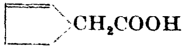
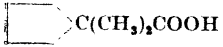
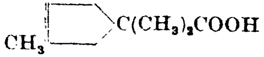
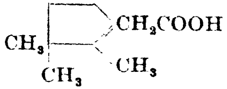
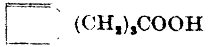
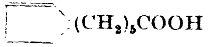
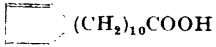
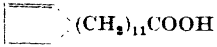
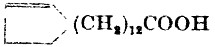
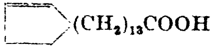
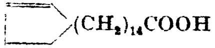
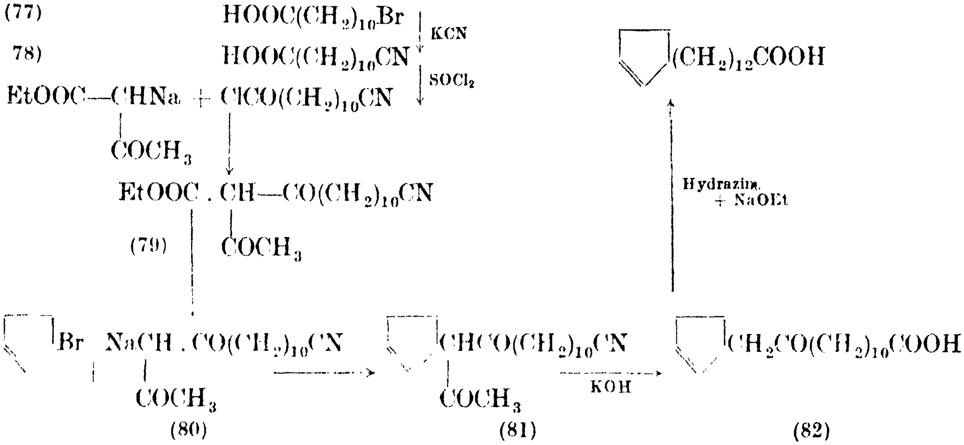
α-*cyclo*Hexenyl-1, propionic acid		—	150°/13 mm.	—
4-Methyl*cyclo*hexenyl-1, acetic acid		41°	138°/14 mm.	—
***cyclo*Heptene-1, carboxylic acid**		54°	260°	126°
***cyclo*Heptene-1, acetic acid**		29°	153°/17 mm.	—
***cyclo*Pentene-1, carboxylic acid**		120°	—	—
3-Methyl*cyclo*pentene-1, carboxylic acid		42°	—	—
2-Methyl*cyclo*pentene-3, carboxylic acid		—	165°/100 mm.	—
2-Methyl*cyclo*pentene-2, carboxylic acid		131°	—	—
1, 2, 3-Trimethyl*cyclo*pentene-2, carboxylic acid	 Laurolenic acid	8°	138°/17 mm.	72°
1, 2, 2-Trimethyl*cyclo*pentene-3, carboxylic acid	 Camphonenic acid	156°	132°/21 mm.	—
2, 2, 3-Trimethyl*cyclo*pentene-3, carboxylic acid	 α-Campolytic acid	38°	128°/2 mm.	—
2, 3, 3-Trimethyl*cyclo*pentene-1, carboxylic acid	 β-Campholytic acid	135°	245°	130°

TABLE X—(*Continued*)

Name	Formula	Acid		Amide
		M.P.	B.P.	M.P.
2-Methyl-5-*iso*propylidene*cyclo*pentene carboxylic acid **Pulegenic acid**		—	146°/9 mm.	122°
***cyclo*-Pentylidene acetic acid**		64°	132°/16 mm.	138°
***cyclo*-Pentenyl-1, acetic acid**		52°	122°/11 mm.	144°
***cyclo*-Pentenyl-2, acetic acid**		—	94°/2·5 mm.	—
***cyclo*-Pentenyl-3, *iso*butyric acid**		54°	145°/14 mm.	155°
3-Methyl-*cyclo*pentenyl-3, *iso*butyric acid Fencholenic acid		—	138°/12 mm.	114°
2, 3, 3-Trimethyl*cyclo*pentenyl-1, acetic acid α-Campholenic acid		53·5°	147°/20 mm.	86°
***cyclo*-Pentenyl-2, butyric acid**		—	126°/4 mm.	—
***cyclo*-Pentenyl-2, caproic acid**		—	152°/4 mm.	—
Hydnocarpic acid		59°	—	112°
Homohydnocarpic acid		57°	—	—
Chaulmoogric acid		68°	—	107°
Homochaulmoogric acid		67°	—	—
Chaulmoogryl acetic acid		73°	—	—

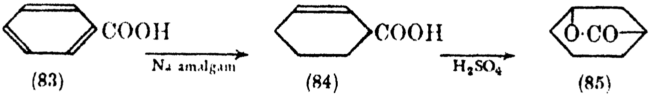
These formulæ indicate the *cyclo*pentene structure (74) for chaulmoogric acid. This has been confirmed by the synthesis of Perkins and Cruz.[1] Undecylenic acid with hydrogen bromide gives ω-bromoundecylic acid (77) and reaction with



potassium cyanide yields the half nitrile of dodecane diacid (78). The acid chloride of the latter, with the sodio derivative of acetoacetic ester yields the ketonic ester (79) and this in turn yields a sodio derivative (80) which with bromo*cyclo*pentene-2 yields a compound (81). This, on boiling with alkali gives keto-chaulmoogric acid (82) capable of reduction by hydrazine and NaOEt to chaulmoogric acid itself.

The use of chaulmoogra and related oils in the treatment of leprosy is no new discovery; its history goes back to antiquity, and modern research has mainly been concerned (*a*) with ascertaining the structures of hydnocapric and chaulmoogric acid, (*b*) obtaining derivatives more specific and better tolerated. On the whole, in spite of the preparation of hundreds of derivatives, the ethyl ester of chaulmoogric acid appears to be the most satisfactory remedial agent for leprosy.

Among the *cyclo*hexene carboxylic acids, *cyclo*hexene-2, carboxylic acid (84) is produced when benzoic acid (83) is reduced with sodium amalgam. Like



most of the acids of this series, it oxidises readily in the air, and in sulphuric acid solution is immediately converted to the lactone (85).

*cyclo*HEXADIENE AND TRIENE CARBOXYLIC ACIDS

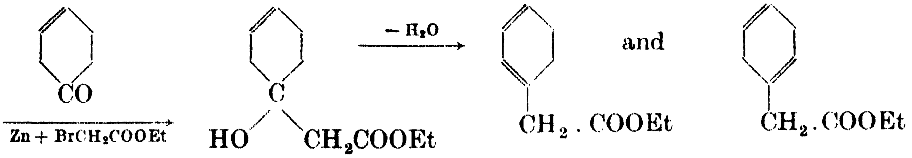
Only a few acids with two double bonds in the nucleus are known, since they are so readily oxidised, even by the most feeble oxidising agents, to the corresponding benzene compound. The commonest method of preparation is to react a cyclic ketone containing one double bond, e.g., *cyclo*hexenone with bromoacetic ester (86) and zinc after the manner of Reformatzski. A hydroxy compound (87) is obtained which can be dehydrated to a mixture of the two esters (88) and (89).[2] Willstätter[3] has prepared a few derivatives of this series,

[1] Perkins and Cruz, *J.A.C.S.*, 1927, **49**, 1070.

[2] Auwers and Peters, *Ber.*, 1910, **43**, 3106.

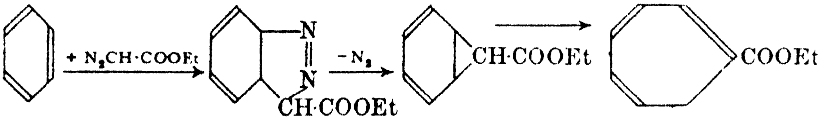
[3] Willstätter, *ibid.*, 1897, **30**, 719.

including a *cyclo*heptadiene carboxylic acid, and Büchner[1] has prepared others the structure of which was determined. Their properties are summarised in Table XI. In addition, the table lists some derivatives of *cyclo*heptatriene.



(86) (87) (88) (89)

The so-called *β-iso*phenyl acetic acid (better called *cyclo*heptatriene-1, 3, 5, carboxylic acid), was obtained during the remarkable experiments of Büchner and Ling[2] in which they observed benzene to condense with diazoacetic ester to give a *nor*caradienic acid (91), presumably *via* the intermediate nitrogen ring compound (90).



(90) (91) (92)

If the *nor*caradienic ester (91) is converted to the amide and heated with alkali the *cyclo*heptatriene 1, 3, 5, carboxylic acid is formed (92).

AROMATIC MONOCARBOXYLIC ACIDS

The entrance of a third double bond into the *cyclo*hexane ring to give *cyclo*-hexatriene, causes an enormous change in the nature of the substance; an almost complete disappearance of those characteristics normally associated with unsaturation and so evident in *cyclo*hexene and *cyclo*hexadiene, and the appearance of that stability and substitutive behaviour usually connoted by the term 'aromatic'. The main discussion of aromatic character is deferred to Chapter VI of Vol. III; the purpose of this chapter is to consider the chemistry of the monocarboxylic acids of the group. They may be divided into the following groups:—

(1) Aromatic acids in which the carboxyl group is directly attached to a benzene ring.
(2) Aromatic acids in which the carboxyl group is directly attached to a polycyclic aromatic structure, e.g., naphthalene, phenanthrene, etc.
(3) Aromatic acids in which the carboxyl group is situated in a side-chain. This chain may be
    (*a*) saturated,
    (*b*) ethylenic,
    (*c*) acetylenic.

The French have applied the very convenient adjectives 'juxtanuclear' to describe members of the first two classes and 'extranuclear' to describe those of the third.

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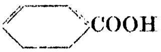
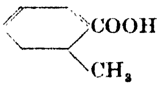
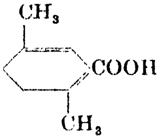
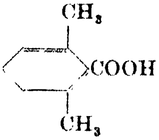
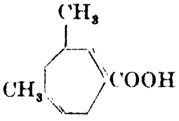
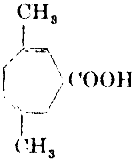
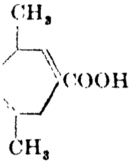
[1] Büchner and Delbruck, *Ann.*, 1908, **358**, 30.
[2] Büchner and Ling, *Ber.*, 1898, **31**, 403.

TABLE XI

SOME MONOCARBOXYLIC ACIDS OF THE *cyclo*ALKADIENE AND *cyclo*ALKATRIENE SERIES

Name	Formula	M.P.	B.P.	Amide M.P.
2, 3-Dihydrobenzoic acid		94·5°	—	—
2-Methyl 2, 3-dihydrobenzoic acid		128°	—	—
2, 5-Dimethyl 3, 4-dihydrobenzoic acid		42°	—	—
2, 6-Dimethyl 3, 4-dihydrobenzoic acid		—	155-60°/28 mm.	—
3, 5-Dimethyl*cyclo*heptadiene-1, 5, carboxylic acid		123°	—	—
3, 6-Dimethyl*cyclo*heptadiene-2, 5, carboxylic acid		40°	—	—
3, 6-Dimethyl*cyclo*heptadiene-1, 5, carboxylic acid		82°	—	—
cyclo-Heptatriene-1,3,5, carboxylic acid	—	71°	—	129°
cyclo-Heptatriene-1,4,6, carboxylic acid	—	56°	—	98°
cyclo-Heptatriene-2,4,6, carboxylic acid	—	32°	—	125·5°

BENZOIC ACID

> "If it be desired to give the salt a shining appearance, it should be dissolved in enough water . . . and . . . quickly filtered, hot . . . into a previously heated flask, when one has the gratification of seeing beautiful crystals shooting out as soon as the solution has become cold."
>
> —CARL WILHELM SCHEELE, 'On salt of benzoin'
> (*Veckoskrift för Läkare och Naturforskare*, 1775, **36**, 128).

The quotation above shows that Scheele was well acquainted with benzoic acid ; indeed, at the time when the Swedish apothecary wrote his paper, benzoic acid, obtained by sublimation from gum benzoin, had been an article of commerce for 150 years. Our true chemical knowledge of benzoic acid dates from the analysis by Liebig and Wöhler in 1832 when they found it to be an oxide of 'benzoyl' (C_7H_6O). They also observed that when 'benzoyl hydride' (benzaldehyde) was treated with alcoholic potash in the absence of air, a decomposition took place with the formation of benzoic acid and a 'new oil', different from the original oil used.[1] It remained for Cannizzaro,[2] just over twenty years later, to recognise the 'new oil' as benzyl alcohol and to remark "This kind of alcohol appears to be the type of a whole class of new alcohols"; it

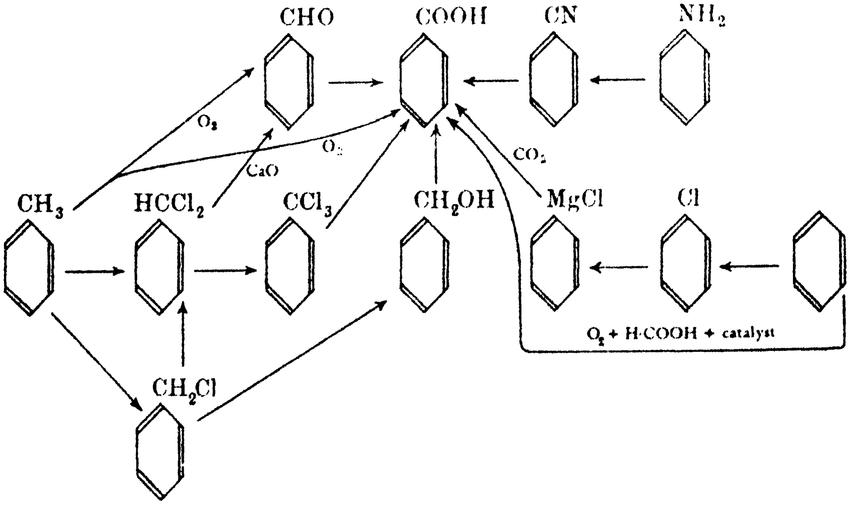
$$R.CHO + R.CHO \longrightarrow R.COOH + R.CH_2OH$$

was in this way that the disproportionation of two molecules of an aromatic aldehyde became associated with the name of Cannizzaro.

Benzoic acid occurs naturally in various plants and in the urine of animals, but only in comparatively small amounts. It is found in the final products of the oxidation of numerous organic compounds and can be obtained in excellent yields by the oxidation of toluene. Indeed, it is noteworthy that this method of obtaining carboxylic acids, by the oxidation of a hydrocarbon, so unsuccessful with simple aliphatic compounds, is eminently satisfactory in the aromatic series. Chromic acid, permanganates and ferricyanides are suitable oxidising agents for the conversion of toluene to benzoic acid, and the process has been extended to the use of atmospheric oxygen in the presence of catalysts, usually oxides of molybdenum, vanadium and manganese. It is usual in manufacturing plants to operate a catalytic toluene oxidation plant for benzaldehyde; a certain amount of benzoic acid is formed simultaneously and usually provides sufficient of this material for market requirements.

Benzaldehyde and benzyl alcohol are readily oxidised to benzoic acid; and indirect methods have been adopted industrially to oxidise toluene, as, for example, the chlorination of that hydrocarbon to benzotrichloride which is hydrolysed by boiling milk of lime to benzoic acid.

Extensive reference (Chap. III) has been made to the Friedel-Crafts method of obtaining carboxylic acids through the acid chlorides. There is also the Sandmeyer method of introducing the —CN group which is hydrolysed readily to the acid. Some of these methods are indicated in the diagram below :—



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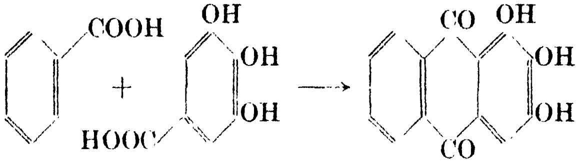
[1] Liebig and Wöhler, *Ann.*, 1832, **3**, 254, 261.

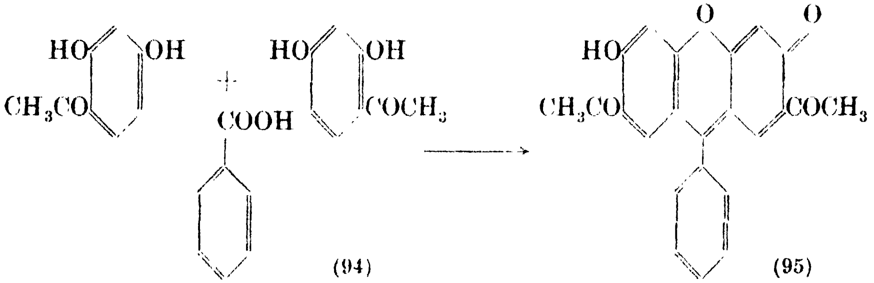
[2] Cannizzaro, *ibid.*, 1853, **88**, 129.

Benzoic acid is a white crystalline solid which is stated to be odourless when pure, the pleasant odour usually associated with the acid being due to a trace of volatile impurity. It melts at 121–124°, but sublimes so readily that the m.p. is difficult to determine.

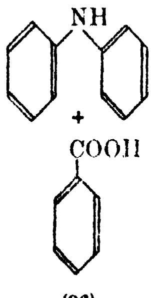
The literature shows that more research has been carried out on benzoic acid than on any other organic acid, but it must be said that in the vast majority of its reactions benzoic acid reacts quite normally, and in itself shows a remarkable stability. In the presence of dehydrating agents, benzoic acid tends to form anthraquinone, a reaction which is catalysed by anhydrous aluminium chloride. Benzoic acid is now only of very restricted use in medicine ; it is used to a limited extent as a preservative, and in the dyestuffs industry. Thus, it condenses with gallic acid to give a trihydroxyanthraquinone (93) which when mordanted with chrome, yields an excellent fast brown (Anthracene Brown). It also catalyses, in an unexplained manner, the phenylation of Rosaniline to Aniline blue. It also condenses with two molecules of resacetophenone (94)[1] to form deeply coloured compounds of the benzein series (95).



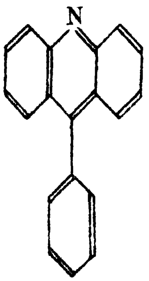
(93)



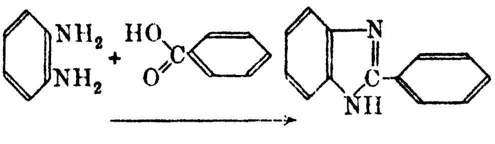
(94) (95)



(96)



(97)



(98) (99)

In the same way diphenylamine[2] (96) gives acridines (97) and *o*-phenylenediamine (98) gives phenylbenzimidazol (99).

The juxtanuclear alkyl benzoic acids are not always easily prepared by the

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[1] Chakravarti, *J.A.C.S.*, 1924, **46**, 382.

[2] Bernthsen, *Ann.*, 1884, **224**, 13.

TABLE XII

THE ALKYL BENZOIC ACIDS

Name	Formula	M.P.	B.P. ethyl ester	B.P. acid chloride	M.P. amide
2-Methyl benzoic acid	$C_6H_4(CH_3)COOH$ 1, 2	102°	219°	110°/29 mm.	143°
3-Methyl benzoic acid	$C_6H_4(CH_3)COOH$ 1, 3	110°	104°/10 mm.	109°/15 mm.	97°
4-Methyl benzoic acid	$C_6H_4(CH_3)COOH$ 1, 4	176°	235°	95°/10 mm.	155°
2, 3-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 2, 3, 1	144°	—	—	—
2, 4-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 2, 4, 1	128°	—	m. 25°	178°
2, 5-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 2, 5, 1	132°	—	m. 26°	186°
2, 6-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 2, 6, 1	116°	—	—	—
3, 4-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 3, 4, 1	164°	—	—	131°
3, 5-Dimethyl benzoic acid	$C_6H_3(CH_3)_2COOH$ 3, 5, 1	170°	241°	—	133°
2, 3, 4-Trimethyl benzoic acid	$C_6H_2(CH_3)_3COOH$ 2, 3, 4, 1	167·5°	—	—	—
2, 4, 5-Trimethyl benzoic acid	$C_6H_2(CH_3)_3COOH$ 2, 4, 5, 1	150°	—	—	—
2, 3, 5-Trimethyl benzoic acid	$C_6H_2(CH_3)_3COOH$ 2, 3, 5, 1	127°	—	—	—
2, 4, 6-Trimethyl benzoic acid	$C_6H_2(CH_3)_3COOH$ 2, 4, 6, 1	150°	—	—	—
3, 4, 5-Trimethyl benzoic acid	$C_6H_2(CH_3)_3COOH$ 3, 4, 5, 1	216°	—	—	—
2, 3, 4, 5-Tetramethyl benzoic acid	$C_6H(CH_3)_4COOH$ 2, 3, 4, 5, 1	169°	—	—	—
2, 3, 4, 6-Tetramethyl benzoic acid	$C_6H(CH_3)_4COOH$ 2, 3, 4, 6, 1	165°	—	—	—
2, 3, 5, 6-Tetramethyl benzoic acid	$C_6H(CH_3)_4COOH$ 2, 3, 5, 6, 1	176°	—	—	—
Pentamethyl benzoic acid	$C_6(CH_3)_5COOH$	210°	—	—	—
2-Ethyl benzoic acid	$C_6H_4(C_2H_5)COOH$ 2, 1	68°	231°	219°	152°
3-Ethyl benzoic acid	$C_6H_4(C_2H_5)COOH$ 3, 1	47°	—	—	—
4-Ethyl benzoic acid	$C_6H_4(C_2H_5)COOH$ 4, 1	110°	—	—	116°

2, 6-Dimethyl, 4-ethyl benzoic acid	$C_6H_2(CH_3)_2(C_2H_5)COOH$ 2, 6, 4, 1	101°	—	—	—
2, 6-Diethyl, 4-methyl benzoic acid	$C_6H_2(C_2H_5)_2(CH_3)COOH$ 2, 6, 4, 1	91°	—	—	—
2, 4, 6-Triethyl benzoic acid	$C_6H_2(C_2H_5)_3COOH$ 2, 4, 6, 1	113°	—	—	—
2-Propyl benzoic acid	$C_6H_4(C_3H_7)COOH$ 2, 1	58°	244–247°	236°	128°
4-Propyl benzoic acid	$C_6H_4(C_3H_7)COOH$ 4, 1	141°	—	—	—
2-*Iso*propyl benzoic acid	$C_6H_4(C_3H_7)COOH$ 2, 1	51°	—	—	—
4-*Iso*propyl benzoic acid	$C_6H_4(C_3H_7)COOH$ (cuminic acid) 4, 1	118°	263–264°	258°	155–160°
4-*ter*-Butyl benzoic acid	$C_6H_4(C_4H_9)COOH$ 4, 1	161°	—	—	171°
4-*ter*-Amyl benzoic acid	$C_6H_4(C_5H_{11})COOH$ 4, 1	158°	—	—	—
4-Methyl, 2-propyl benzoic acid	$C_6H_3(CH_3)(C_3H_7)COOH$ 4, 2, 1	76°	—	—	—
4-Methyl, 3-propyl benzoic acid	$C_6H_3(CH_3)(C_3H_7)COOH$ 4, 3, 1	89–92°	—	—	—
2-Methyl, 5-*iso*propyl benzoic acid	$C_6H_3(CH_3)C_3H_7)COOH$ 2, 5, 1	72°	—	132°/18 mm.	147°
3-Methyl, 6-*iso*propyl benzoic acid	$C_6H_3(CH_3)(C_3H_7)COOH$ 3, 6, 1	84°	142°/13 mm.	129°/13 mm.	138°
2-Methyl, 6-*ter*-Butyl benzoic acid	$C_6H_3(CH_3)C_4H_9)COOH$ 2, 6, 1	132°	—	—	—
2-Methyl, 4-*ter*-Butyl benzoic acid	$C_6H_3(CH_3)C_4H_9)COOH$ 2, 4, 1	140°	—	—	—
4-Methyl, 2-*ter*-Butyl benzoic acid	$C_6H_3(CH_3)(C_4H_9)COOH$ 4, 2, 1	167°	—	—	—
3-Methyl, 5-*ter*-Butyl benzoic acid	$C_6H_3(CH_3)(C_4H_9)COOH$ 3, 5, 1	162°	—	—	—
Diphenyl, 2-carboxylic acid	$C_6H_5 . C_6H_4 . COOH$	114°	—	—	—
Diphenyl, 3-carboxylic acid	$C_6H_5 . C_6H_4 . COOH$	159°	—	—	—
Diphenyl, 4-carboxylic acid	$C_6H_5 . C_6H_4 . COOH$	224°	—	—	—
4′-Methyl diphenyl, 2-carboxylic acid	$CH_3 . C_6H_4 . C_6H_4 . COOH$	179°	—	—	—
4′-Methyl diphenyl, 4-carboxylic acid	$CH_3 . C_6H_4 . C_6H_4 . COOH$	243°	—	—	—
Diphenyl methane, 2-carboxylic acid	$C_6H_5 . CH_2 . C_6H_4 . COOH$	117°	—	—	—
Diphenyl methane, 3-carboxylic acid	$C_6H_5 . CH_2 . C_6H_4 . COOH$	108°	—	—	—
Diphenyl methane, 4-carboxylic acid	$C_6H_5 . CH_2 . C_6H_4 . COOH$	158°	—	—	—

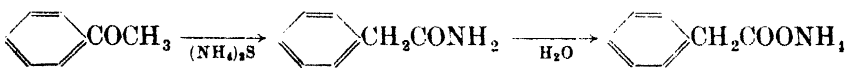
oxidation of the appropriate hydrocarbon, since this process involves the fractional oxidation of the side-chains. It is often possible to achieve this by careful control of the oxidising agent and conditions, as, for example, in the oxidation of *o*-xylene to *o*-toluic acid by boiling neutral permanganate. In many cases it is almost essential to pass through the stage of the nitrile, prepared by Sandmeyer's method from the appropriate amine.

One or two unusual methods of synthesis stand out; such as Geuther and Frohlich's [1] synthesis of 3, 5-dimethylbenzoic acid when sodium methylate and sodium acetate are heated in a current of carbon dioxide, and the method of Frey and Horowitz [2] in which a substantial proportion of 2, 4-dimethylbenzoic acid is obtained when acetyl chloride reacts with *m*-xylene in the presence of anhydrous aluminium chloride.

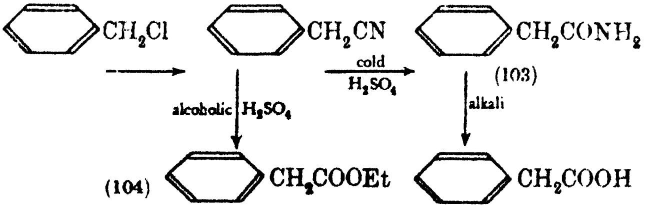
The properties of the alkyl benzoic acids and their simple derivatives have been collected together into Table XII, which has been made fairly complete on account of the frequency with which these acids are met in practical work.

EXTRANUCLEAR AROMATIC MONOCARBOXYLIC ACIDS

Phenylacetic acid, $C_6H_5CH_2COOH$ is not easy to prepare in good yield. Industrially it is probably best prepared by heating acetophenone (100) under pressure with ammonium sulphide. This reaction, often called 'Willgerodt's reaction',[3] is obscure in its mechanism but yields a mixture of phenylacetamide (101) and ammonium phenyl acetate (102). Yields up to 60–70 per cent. of phenylacetyl compounds can be obtained by this method, but the reaction is less satisfactory when the methyl group is replaced by other and larger alkyl groups. The chief alternative method for preparing phenylacetic acid is to convert benzyl chloride to the cyanide and to hydrolyse the latter to the acid. By using sulphuric acid in the cold, phenylacetamide can be isolated as an intermediate stage (103), and with alcoholic sulphuric acid, ethyl phenylacetate is obtained (104). The ready accessibility of phenylacetaldehyde from *cyclo*-öctatetrene (p. 129) makes the industrial synthesis of phenylacetic acid feasible from this source.



(100) (101) (102)



Phenylacetic acid has a persistent and somewhat pleasant smell, and is usually met with in the form of large white plates. It is used fairly extensively for the preparation of buffer solutions, which are stable, and unaffected by the growth of moulds. To prepare such buffers a saturated solution of phenylacetic acid in water is treated with N/100 alkali in the following proportions :—

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[1] Geuther and Frohlich, *Ann.*, 1880, **202**, 310.

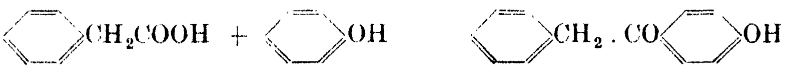
[2] Frey and Horowitz, *J. Prak. Chem.*, 1891, 2 **43**, 119.

[3] Willgerodt *et al.*, *J. Prak. Chem.*, 1909, 2 **80**, 183, 192; 1910, 2 **81**, 74, 384.

TABLE XIII

*p*H	Quantities of solutions	
	Sat. aq. acid	N/100 alkali
3·16	100	nil
3·45	95	5
3·56	90	10
3·78	80	20
4·0	70	30
4·14	60	40
4·31	50	50
4·47	40	60
4·66	30	70

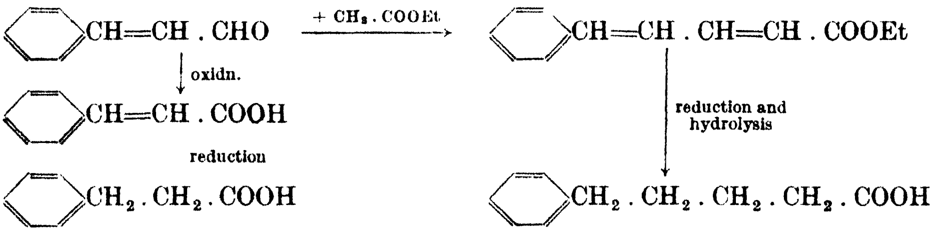
In many ways phenyl acetic acid behaves as an aliphatic acid. It parts with carbon dioxide quite readily when heated in glycerin to give toluene ; and condenses readily with phenols to give hydroxydesoxybenzoin [1] (105)



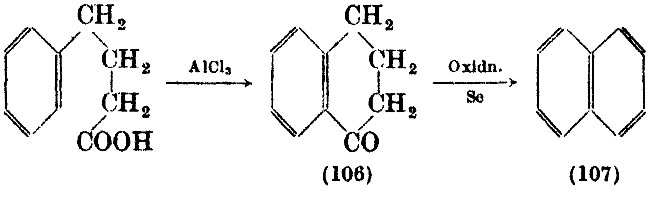
(105)

The methylene group reacts readily and is oxidised by selenium dioxide to the keto group giving phenylglyoxylic acid. The hydrogen of the methylene group is replaceable by sodium, permitting the formation of derivatives by reaction with alkyl halides.

The whole series of acids up to $C_6H_5(CH_2)_9COOH$ is known and their properties are summarised in Table XIV. The first member of the series, after phenylacetic acid, namely, phenyl propionic acid, is obtained by the reduction of cinnamic acid, just as many of the higher acids are obtained by complete saturation of the compounds obtained by condensing cinnamic aldehyde with esters, e.g.,



One peculiarity of the acid chloride of phenyl butyric acid is that it suffers an internal condensation in the presence of anhydrous aluminium chloride to form ketotetrahydronaphthalene (106) ; this can, of course, be converted to naphthalene itself (107). The reaction applied to toluic and other substituted acids leads to



(106) (107)

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[1] Weisl, *Monatsh.*, 1905, **26**, 984.

TABLE XIV

SOME EXTRANUCLEAR AROMATIC MONOCARBOXYLIC ACIDS

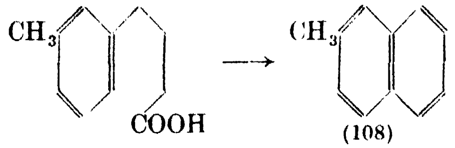
Name	Formula	M.P.	B.P. ethyl ester	B.P. acid chloride	M.P. amide
Phenylacetic acid	$C_6H_5 . CH_2 . COOH$	78°	227°	105°/23 mm.	157°
Phenyl propionic acid	$C_6H_5(CH_2)_2COOH$	48°	127°/15 mm.	115°/12 mm.	105°
Phenyl butyric acid	$C_6H_5(CH_2)_3COOH$	51°	—	—	—
Phenyl valeric acid	$C_6H_5(CH_2)_4COOH$	59°	150°/11 mm.	—	109°
Phenyl caproic acid	$C_6H_5(CH_2)_5COOH$	b. 208°/30 mm.	163°/13 mm.	162°/12 mm.	—
Phenyl heptoic acid	$C_6H_5(CH_2)_6COOH$	b. 210°/17 mm.	176°/17 mm.	167°/11 mm.	89°
Phenyl caprylic acid	$C_6H_5(CH_2)_7COOH$	b. 210°/14 mm.	—	—	—
Phenyl pelargonic acid	$C_6H_5(CH_2)_8COOH$	41°	220–224°/20 mm.	—	—
o-Tolyl acetic acid	$C_6H_4(CH_3)CH_2COOH$	88°	—	—	161°
m-Tolyl acetic acid	$C_6H_4(CH_3)CH_2COOH$	61°	238°	136°/15 mm.	141°
p-Tolyl acetic acid	$C_6H_4(CH_3)CH_2COOH$	92–94°	240°	—	184°
2, 4-Dimethylphenyl acetic acid	$C_6H_3(CH_3)_2CH_2COOH$	101°	—	—	183°
3, 5-Dimethylphenyl acetic acid	$C_6H_3(CH_3)CH_2 . COOH$	100°	—	—	—
o-Ethylphenyl acetic acid	$C_6H_4(C_2H_5)CH_2 . COOH$	83·5°	—	—	—
m-Ethylphenyl acetic acid	$C_6H_4(C_2H_5)CH_2COOH$	62–64°	—	—	—
p-*iso*-Propylphenyl acetic acid	$C_6H_4(C_3H_7)CH_2 . COOH$	52°	265°	—	170°
Mesityl acetic acid	$C_6H_2(CH_3)_3CH_2 . COOH$	168°	—	—	208°
α-Methylphenyl acetic acid	$C_6H_5CH(CH_3)COOH$	b. 160°/25 mm.	230°	97°/12 mm.	91°
α-Ethylphenyl acetic acid	$C_6H_5CH(C_2H_5)COOH$	42°	—	—	—

α-*n*-Propyl phenyl acetic acid	$C_6H_5CH(C_3H_7)COOH$		52°	—	—	—
α-*iso*-Propyl phenyl acetic acid	$C_6H_5CH(C_3H_7)COOH$		58–59°	—	—	68°
αα-Dimethylphenyl acetic acid	$C_6H_5C(CH_3)_2COOH$		78°	253–256°	109°/13 mm.	160–161°
o-Tolyl propionic acid	$C_6H_4(CH_3)CH_2CH_2COOH$		102°	—	—	—
m-Tolyl propionic acid	$C_6H_4(CH_3)CH_2CH_2COOH$		42°	—	—	—
p-Tolyl propionic acid	$C_6H_4(CH_3)CH_2CH_2COOH$		117°	263–264°	—	135°
α-Phenyl acrylic acid	$C_6H_5 . C(=CH_2)COOH$ (Tropic acid)		105–107°	—	—	122°
β-Phenyl acrylic acid	$C_6H_5 . CH=CH . COOH$ (Cinnamic acid) *	*trans-* *cis-*	— —	m. 36° b. 49°/0·1 mm.	123°/8 mm. —	148° —
4-Phenyl-butene-3, acid	$C_6H_5 . CH=CH . CH_2COOH$	*cis-* *trans-*	liquid 86°	— —	— —	86° 130°
4-Phenyl-butene-2, acid	$C_6H_5 . CH_2CH=CH . COOH$		65°	—	—	—
5-Phenyl-pentene-4, acid	$C_6H_5 . CH=CHCH_2CH_2COOH$		90°	—	—	—
5-Phenyl-pentene-3, acid	$C_6H_5 . CH_2 . CH=CH . CH_2COOH$		31°	—	—	—
5-Phenyl-pentene-2, acid	$C_6H_5 . CH_2CH_2CH=CH . COOH$		104°	—	—	—
Phenyl propiolic acid	$C_6H_5 . C\equiv C . COOH$		136°	137°/13 mm.	119°/12 mm.	106°
α-Phenylcinnamic acid	$C_6H_5 . CH=C(C_6H_5)COOH$	*cis-* *trans-*	172° 137°	— —	— —	— —
β-Phenylcinnamic acid	$(C_6H_5)_2C=CH . COOH$		162°	—	—	—
Diphenyl acetic acid	$(C_6H_5)_2CH . COOH$		145°	m. 58°	m. 56°	168°
Triphenyl acetic acid	$(C_6H_5)_3C . COOH$		265°d.	121°	129°	238°
α-Naphthoic acid	$C_{10}H_7 . COOH$		161°	—	—	—
β-Naphthoic acid	$C_{10}H_7 . COOH$		184°	—	—	—
Phenanthrene-1-carboxylic acid	$C_{14}H_9 . COOH$		233°	—	—	—

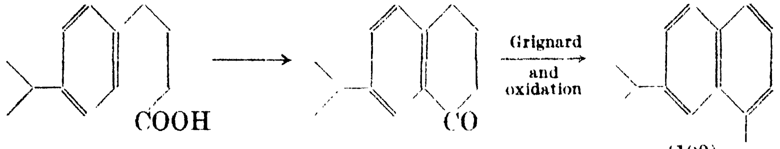
---

* Cinnamic acid appears to exist in 6 forms, 4 *cis-* (m. 68°, 58°, 142°, ?) and two *trans-*, both m. 133°.

the formation of substances difficult to obtain otherwise, such as β-methyl naphthalene (108) and eudalene (109).

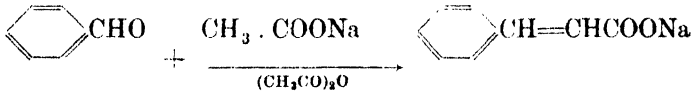


(108)

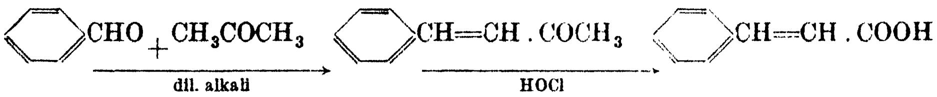


(109)

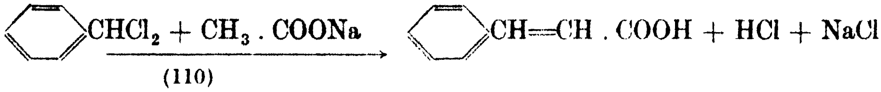
Of the other acids listed in Table XIV, cinnamic acid stands out as of paramount importance. Dumas and Peligot[1] first recognised the substance as a new acid in 1834, and it was soon recognised as widely distributed in nature. It is present in liquid storax and in Peruvian and Tolu balsams. It is also found in the flowers of many varieties and species of *Globularia*. The artificial preparation of cinnamic acid is always associated with the Perkin reaction, Perkin[2] being the discoverer of the reaction whereby cinnamic acid is obtained by the condensation of benzaldehyde and sodium acetate in the presence of acetic anhydride. The mechanism of this reaction has been the subject of much speculation (see also Chap. IX, Vol. III), but the *net* result is as shown by the equation



This reaction is now only of historical and theoretical interest as cinnamic acid is made industrially by condensing benzaldehyde and acetone and oxidising the benzalacetone with hypochlorous acid



Alternatively, benzal chloride[3] and sodium acetate (110) are autoclaved at 180°



(110)

There are also numerous syntheses of cinnamic acid which are of interest but little practical importance; some of these are :—

1. The Claisen reaction between benzaldehyde and ethyl acetate.
2. The slow distillation of diphenyl fumarate.
3. The action of carbon dioxide on the Grignard compound of styryl bromide.
4. The pyrogenic monomerisation of the truxillic acids.

The cinnamic acid referred to in these remarks is the *trans*- form. It exists in two forms, both of which melt at 133°, the β- form is produced from the α-

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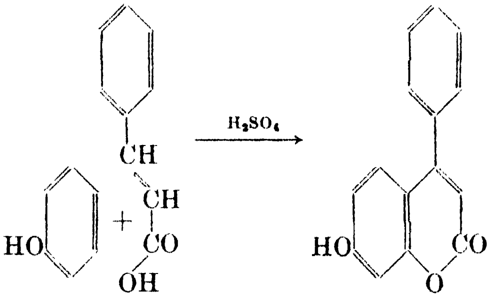
[1] Dumas and Peligot, *Ann.*, 1835, **14**, 50.
[2] Perkin, *J.C.S.*, 1877, **31**, 838.
[3] Ullmann, " Enzyklopädie d. Tech. Chem.", 1921, IX, 613.

or ordinary form[1] by sulphuric acid. The solid *trans*-cinnamic acid is converted to truxillic acids by ultra-violet irradiation[2] but in solution the *cis*-isomer is formed.

Chemically, cinnamic acid behaves as an α-unsaturated aliphatic acid, adding reagents normally to the double bond and giving the normal acid derivatives such as ester, amide, etc. An anomalous reaction is observed with iodine which gives α-iodo-β-phenylacrylic acid.

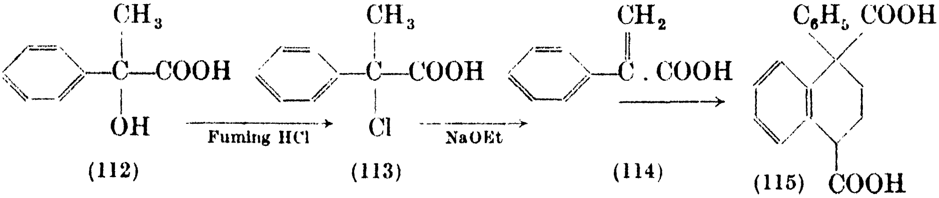
The formation of fused-ring compounds from cinnamic acid is of importance; with phenols and concentrated sulphuric acid derivatives of coumarin[3] are obtained. Thus phenol itself gives 7-hydroxy-4-phenyldihydrocoumarin (111)



(111)

cis-Cinnamic acid (*allo*cinnamic acid) is best obtained from phenylpropiolic acid by catalytic reduction with hydrogen and palladium, or by the irradiation of a benzene solution of the *trans-* form.

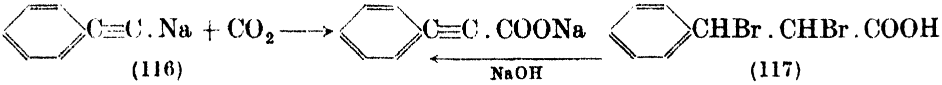
Tropic acid (114), was originally obtained by Lossen[4] from the alkaloids atropine and hyoscyamine by boiling with baryta-water, and was synthesised from atrolactic acid (112) by the steps indicated below :—



(112) (113) (114) (115)

It is a white crystalline solid, distilling at 267°, and being converted to isatropic acid (1-phenyl tetrahydronaphthalene, 1, 4-dicarboxylic acid) (115) on prolonged heating.

In the acetylenic series, phenyl propiolic acid is almost the only compound of importance. Prepared originally by Glaser[5] by the action of carbon dioxide on sodiophenylacetylene (116) it is more conveniently prepared from dibromocinnamic acid (117) and alcoholic alkali.



(116) (117)

Phenyl propiolic acid, a white crystalline substance, m. 136°, is a fairly strong acid, $K = 5{\cdot}9 \times 10^{-3}$. It gives a chloride normally, but this passes straight to the nitrile with ammonia, the amide being prepared from the ethyl ester. It shows intense reactivity,—adding water with sulphuric acid to give benzoyl acetic acid (118) combining with phenylhydrazine to give a pyrazolone (121) and with hydroxylamine to give an oxazolone (119); acetone yields a pyrone (120), whilst with tetraphenyl*cyclo*pentadienone (122) it gives pentaphenyl benzoic acid; most of these reactions are illustrated below :—

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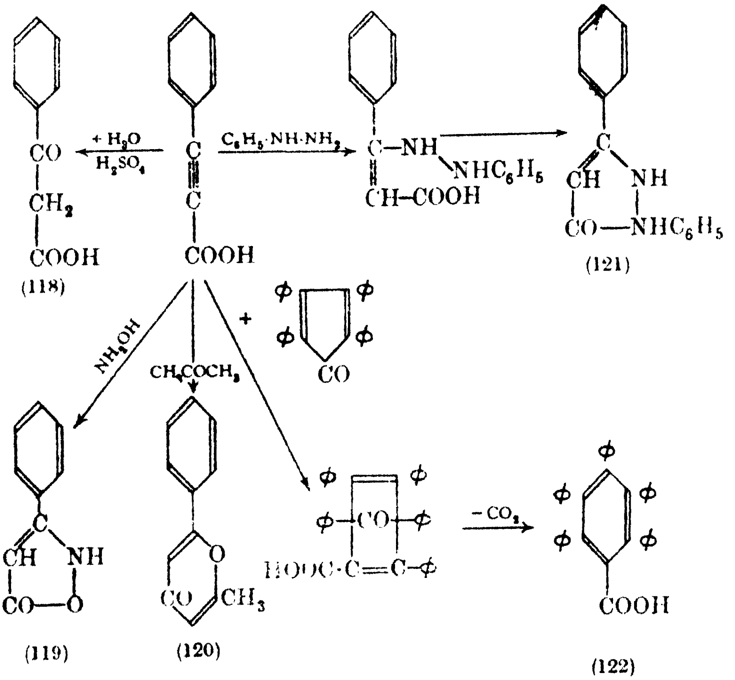
[1] Rupe and Bleschschmidt, *J. Pr. Chem.*, 1917, **96**, 59.

[2] Stobbe and Lehfeldt, *Ber.*, 1925, **58**, 2415.

[3] Kostanecki, *ibid.*, 1887, **20**, 3141.

[4] Lossen, *Ann.*, 1866, **138**, 233.

[5] Glaser, *ibid.*, 1870, **154**, 140.



Numerous monocarboxylic acids are known which are derived from hydrocarbons with fused rings or more than one aromatic group, but it is not proposed to deal systematically with them; they are referred to in Table XIV, and in various other parts of this volume.

THE DIBASIC ACIDS

The simple dibasic acids are nearly all known by trivial names attached to them in early times, when their constitution was unknown; most of these names arise from the substances from which the acids were extracted—' oxalic ' from *Oxalis acetosella*; ' succinic ' from ' succinum ' (L. amber); ' adipic ' from ' adeps ' (L. fat), etc. Systematic nomenclature derives the name of dibasic acids from that of the corresponding normal hydrocarbon, with the addition of the term ' diacid ', to indicate that the terminal carbon atoms are converted to carboxylic groups. This nomenclature is given in full in Table XV, and is very convenient for acids with more than six carbon atoms for which the trivial names are difficult to remember.

It will be observed from the data given in Table XV that there are two distinct dissociation constants, and that in general the dibasic acids are stronger acids than the corresponding monobasic acids. Oxalic acid is anomalous in that it exists in solution mainly as the ortho- acid $(HO)_3C\,.\,C(OH)_3$—thus affording another illustration of the tendency shown by substances containing two adjacent carbonyl groups to combine with water; it is probably this structure that gives oxalic acid its abnormally high dissociation constant.

TABLE XV

Name of acid	Systematic name	Formula	M.P.	Dissociation Constants	
				$K_1 \times 10^5$	$K_2 \times 10^6$
Oxalic	Ethane diacid	$(COOH)_2$	189·5°	5800	64
Malonic	Propane diacid	$CH_2(COOH)_2$	135·6°	149	2·0
Succinic	Butane diacid	$C_2H_4(COOH)_2$	185°	6·4	3·3
Glutaric	Pentane diacid	$C_3H_6(COOH)_2$	97·5°	4·5	3·8
Adipic	Hexane diacid	$C_4H_8(COOH)_2$	151°	3·8	3·9
Pimelic	Heptane diacid	$C_5H_{10}(COOH)_2$	105·5°	3·3	3·8
Suberic	Octane diacid	$C_6H_{12}(COOH)_2$	144°	3·0	4·0
Azelaic	Nonane diacid	$C_7H_{14}(COOH)_2$	107°	2·8	3·9
Sebacic	Decane diacid	$C_8H_{16}(COOH)_2$	134°	2·8	—
—	Undecane diacid	$C_9H_{18}(COOH)_2$	111°	—	—
—	Dodecane diacid	$C_{10}H_{20}(COOH)_2$	128°		—
Brassylic	Terdecane diacid	$C_{11}H_{22}(COOH)_2$	113°	—	—
—	Tetradecane diacid	$C_{12}H_{24}(COOH)_2$	126°	—	—
—	Pentadecane diacid	$C_{13}H_{26}(COOH)_2$	115°	—	—
Thapsic	Hexadecane diacid	$C_{14}H_{28}(COOH)_2$	125°	—	—
—	Heptadecane diacid	$C_{15}H_{30}(COOH)_2$	118°	—	—
—	Octadecane diacid	$C_{16}H_{32}(COOH)_2$	125°	—	—
Japanic	Nonadecane diacid	$C_{17}H_{34}(COOH)_2$	119°	—	—
—	Eicosane diacid	$C_{18}H_{36}(COOH)_2$	124°	—	—
—	Heneicosane diacid	$C_{19}H_{38}(COOH)_2$	123°	—	—
—	Docosane diacid	$C_{20}H_{40}(COOH)_2$	124°	—	—
—	Tricosane diacid	$C_{21}H_{42}(COOH)_2$	127·5°	—	—
—	Tetracosane diacid	$C_{22}H_{44}(COOH)_2$	128°	—	—
—	Hexacosane diacid	$C_{24}H_{48}(COOH)_2$	123·5°	—	—
—	Triacontane diacid	$C_{28}H_{56}(COOH)_2$	123°	—	—
—	Dotriacontane diacid	$C_{30}H_{60}(COOH)_2$	123°	—	—

Much of our knowledge of the higher dibasic acids is due to the work of Chuit, who synthesised most of the dibasic acids from C_7 to C_{28} in connexion with Ruzicka's work on the large-ring ketones (see also Appendix to Chap. VI).

OXALIC ACID

Oxalic acid is very frequently the penultimate stage in the drastic oxidation of organic substances, being, next to carbon dioxide, the organic substance containing most oxygen. As such it was frequently isolated during early experiments on the action of fuming nitric acid on sugars, starches and gums; the action of nitric acid on sugar constituted the first method by which industrial quantities of oxalic acid were obtained. Scheele obtained oxalic acid from sorrel (*Oxalis*), and showed it to be identical with 'acid of sugar' (i.e., the acid obtained by the oxidation of sugar with nitric acid). Oxalic acid and its salts are fairly widely distributed in Nature, being present in the urine of mammalia as the calcium salt, whilst the acid potassium salt is to be found in the *Oxalis* and *Rumex* families of plants. Sodium, calcium and magnesium salts are also found in plants.

The earliest method used industrially for producing oxalic acid was the oxidation of sugar with nitric acid. This proving uneconomic, in 1856 John Dale of Manchester developed a process based on an observation of Gay-Lussac,[1] in which sawdust impregnated with a mixture of caustic soda and potash was heated to about 200° on iron plates. A complex reaction takes place with the formation of sodium and potassium oxalates. The crude mass yields about 20 per cent. of anhydrous oxalic acid, and is worked up by extraction. Soft woods yield more oxalic acid than hard woods, and pine-sawdust was most esteemed in this process.

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[1] Gay-Lussac, *Ann. Chim. Phys.*, 1829, **41**, 398.

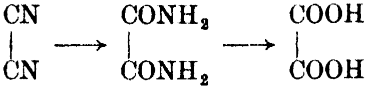
The advent of cheap sodium formate, made from carbon monoxide and alkali has reversed the older procedure of manufacturing formic from oxalic acid, and most of the latter commodity finding its way into commerce is obtained by heating sodium formate under reduced pressure to about 400° when the

$$2H \,.\, COONa \longrightarrow (COONa)_2 + H_2$$

reaction proceeds substantially, and leaves behind a crude sodium oxalate which is the main source of industrial oxalic acid and oxalates. Oxalates are also obtained in substantial yield when carbon dioxide is passed over sodium heated to 360° :—

$$2CO_2 + 2Na \longrightarrow (COONa)_2$$

From a constitutional standpoint, the progressive hydrolysis of cyanogen to oxalic acid is of interest ; oxamide is first formed and on prolonged action the acid itself can be obtained :—



$$\begin{array}{l} CN \\ | \\ CN \end{array} \longrightarrow \begin{array}{l} CONH_2 \\ | \\ CONH_2 \end{array} \longrightarrow \begin{array}{l} COOH \\ | \\ COOH \end{array}$$

Concentrated hydrochloric acid may be used for this series of reactions, which leads us to consider cyanogen as the true dinitrile [1] of oxalic acid. Oxalic acid may also be obtained by the oxidation of glycol by nitric acid of 50 per cent. strength.

Although oxalic acid crystallises with two molecules of water and exists in aqueous solution as the ortho- acid $(HO)_3C \,.\, C(OH)_3$, it readily loses its water on heating yielding an anhydrous acid ; complete dehydration can be attained at 100°. The anhydrous acid forms its acid chloride, oxalyl chloride, $(COCl)_2$ normally.

The reactions of oxalic acid are not of outstanding synthetic interest, as it is an end-product, rather than a source. Oxalic acid forms both acid and normal salts, the former often crystallising with one additional molecule of the ortho- acid ; thus, potassium tetroxalate, $KHC_2O_4 \,.\, H_2C_2O_4 \,.\, 2H_2O$, is such a complex, and is a valuable standard in analytical procedure, being capable of acting as an acidimetric and oxidation standard, and being at the same time capable of easy purification and of storage in an unaltered condition. Oxalic acid is very easily esterified and condenses rapidly with amines ; its diethyl ester forms oxamide $(CO \,.\, NH_2)_2$ almost quantitatively on treatment with ammonia.

Malonic Acid.—Although it occurs naturally in beetroot, Dessaignes [2] first obtained malonic acid in 1858 by the oxidation of natural malic acid with potassium dichromate. Like oxalic acid, although less frequently, malonic acid is found as an end-product in oxidative degradation ; Baeyer, for example, found it in the products of oxidation of uric acid.[3] Its synthesis was achieved simultaneously by Kolbe and Müller by the hydrolysis of cyanacetic acid. It is by this method that malonic acid itself has been made since that time ; chloroacetic acid is converted to cyanacetic acid and the solution warmed with caustic soda to hydrolyse the —CN group. On evaporating to dryness and extracting with ether, malonic acid is obtained. It is a colourless, highly crystalline acid, readily soluble in water. By variants of the above reaction, mainly involving the esterification of the acid in alcoholic solution, diethyl malonate is obtained ; the chemistry of this ester is discussed in Appendix II to this chapter.

Malonic acid is itself distinguished by unusual activity of the methylene group, and its reaction with aldehydes is a valuable method in the synthesis of unsaturated acids. Thus crotonic and sorbic acids can readily be obtained from malonic acid by condensation of acetaldehyde and crotonaldehyde respectively, in the presence of pyridine, followed by decarboxylation, which in the case of the latter example takes place spontaneously at water-bath temperature. The reactions are as follows :—

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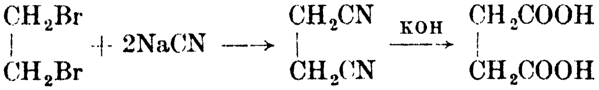
[1] Hultmann and Davis, *J.A.C.S.*, 1921, **43**, 366.

[2] Dessaignes, *C.R.*, 1858, **47**, 76 ; *Ann.*, 1858, **107**, 251.

[3] Baeyer, *ibid.*, 1864, **130**, 143.

$$\begin{aligned} CH_3\,.\,CHO + CH_2(COOH)_2 &\longrightarrow CH_3\,.\,CH{=}C(COOH)_2 \\ &\longrightarrow CH_3\,.\,CH{=}CH\,.\,COOH \\ CH_3\,.\,CH{=}CH\,.\,CHO + CH_2(COOH)_2 &\longrightarrow CH_3\,.\,CH{=}CH\,.\,CH{=}C(COOH)_2 \\ &\longrightarrow CH_3\,.\,CH{=}CH\,.\,CH{=}CH\,.\,COOH \end{aligned}$$

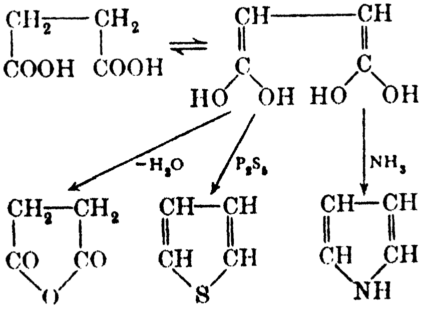
Succinic Acid.—Succinic acid and its salts are widely distributed in natural substances ; thus, calcium succinate crystals are found in the bark of the mulberry tree, and the acid itself is found in nearly all *papaveraceæ*, and *chelidonium* species ; it has also been identified in lettuce and many other plants. A basic aluminium succinate is found as a crystalline deposit in the Australian tree *Orites excelsa*. Its formation from amber by dry distillation has been known for many generations, and gives rise to the name, Agricola and Libavius both describing this method of preparation, the latter referring to succinic acid in 1595 as ' Flos succini '. The distillation of waste amber chips has been a commercial method of preparing succinic acid for many years ; the method was replaced by fermentation processes, first described in crude form by Beissenhirtz [1] in 1818 and later improved so as to form the basis of an industrial process. A very large variety of fermentations produce succinic acid in substantial yield and many others such as the familiar acetic and alcoholic fermentations yield small amounts. Any substance such as malic, tartaric, maleic or aspartic acid is converted by some yeasts and bacteria to succinic acid by reduction. Ammonium tartrate has been used in this way as an industrial source of succinic acid, being subjected to fermentation. The process takes about eight weeks, during which time the tartaric acid disappears and is replaced by about one quarter of its weight of succinic acid. The most satisfactory method of obtaining succinic acid in quantity is by the hydrolysis of succindinitrile (123), obtainable in quantity by reacting ethylene dibromide with sodium cyanide ;



$$\begin{array}{l} CH_2Br \\ | \\ CH_2Br \end{array} + 2NaCN \longrightarrow \begin{array}{l} CH_2CN \\ | \\ CH_2CN \end{array} \xrightarrow{KOH} \begin{array}{l} CH_2COOH \\ | \\ CH_2COOH \end{array}$$

(123)

The chemistry of succinic acid, as an acid, is not particularly striking, except for the tendency which it exhibits to form ring compounds. Thus, ammonium succinate distilled with zinc dust yields pyrrole ; with phosphorus pentasulphide, thiophen is formed, and on distillation alone, succinic anhydride is obtained :—



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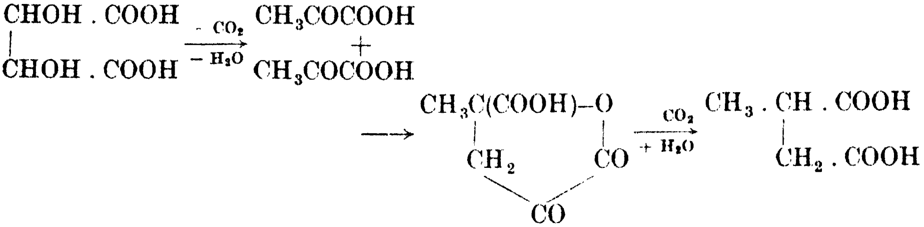
[1] Beissenhirtz, Berlin, Jahres, 1818, 158.

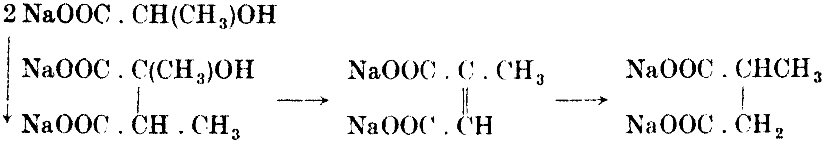
Succinic anhydride is best obtained by the action of acetic anhydride on sodium succinate; it is a beautifully crystalline substance (m. 119·6°).

Derivatives of Succinic Acid.—A number of alkyl derivatives of succinic acid are known, chief amongst which is methylsuccinic or pyrotartaric acid, the latter name being sufficient indication of the method by which it is prepared. The mechanism of its formation from tartaric acid by pyrolysis is stated[1] to be due to the intermediate formation of pyruvic acid, and of a ketovalerolactone (124) which on loss of carbon dioxide and addition of water yields methylsuccinic acid:—



(124)

Ipatiev and Rasuwajev[2] obtained a good yield of methylsuccinic acid by the action of hydrogen under pressure on solutions of sodium lactate. They postulate the following sequence of reactions:—

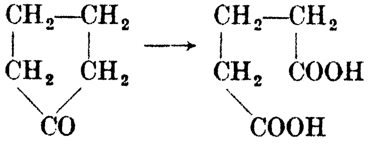


$$
\begin{array}{l}
2\,\mathrm{NaOOC\,.\,CH(CH_3)OH}\\
\downarrow\;
\begin{array}{l}\mathrm{NaOOC\,.\,C(CH_3)OH}\\ \quad|\\ \mathrm{NaOOC\,.\,CH\,.\,CH_3}\end{array}
\longrightarrow
\begin{array}{l}\mathrm{NaOOC\,.\,C\,.\,CH_3}\\ \quad\|\\ \mathrm{NaOOC\,.\,CH}\end{array}
\longrightarrow
\begin{array}{l}\mathrm{NaOOC\,.\,CHCH_3}\\ \quad|\\ \mathrm{NaOOC\,.\,CH_2}\end{array}
\end{array}
$$

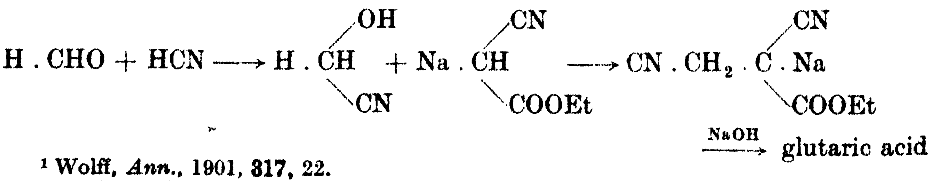
Methane was isolated during the reaction.

Methylsuccinic acid is the first acid of this series to exhibit an asymmetric carbon atom; the racemic form, m. 112°, can be separated through the strychnine salt; the acid readily forms an anhydride (m. 37°; b. 239°).

Glutaric Acid.—During an examination of naturally occurring glutamic acid, Dittmar in 1872[3] transformed it successively into hydroxyglutamic and glutaric acids, and two years later Reboul[4] and Markownikov,[5] independently, obtained glutaric acid by the hydrolysis of trimethylene dicyanide. Since then it has been obtained by a number of other methods, outstanding among which is the action of formaldehyde on malonic ester in the presence of bases such as piperidine or diethylamine. Other methods of interest are the oxidation with nitric acid of *cyclo*pentanone:—



and the condensation of formaldehyde, hydrocyanic acid and the sodio derivative of cyanacetic ester:—



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[1] Wolff, *Ann.*, 1901, **317**, 22.

[2] Ipatiev and Rasuwajev, *Ber.*, 1927, **60**, 1971, 1973, 1976.

[3] Dittmar, *J. Prakt. Chem.*, 1872, **5**, 338.

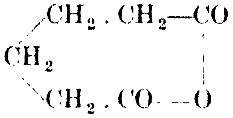
[4] Reboul, *C.R.*, 1876, **82**, 1197.

[5] Markownikov, *Ann.*, 1876, **182**, 341.

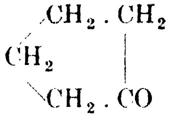
Glutaric acid is easily soluble in water, 100 c.c. of saturated solution at 20° containing 63 grams of the acid. It forms large monoclinic prisms, m. 97·5°. Chemically, glutaric acid gives the various reactions of dibasic acids in a normal fashion ; it has a comparatively insoluble zinc salt, by which it may be identified or estimated, and its silver salt gives butyrolactone on treatment with iodine. Like succinic acid it forms a cyclic anhydride and imide (m. 57° and 151° respectively). Glutaric acid occurs naturally in beet and allied roots, and also in the sweat of sheep ; it may be recovered from the aqueous rinsings of sheep's wool during cleansing.

Adipic Acid.—Laurent's discovery of adipic acid in 1837, by the oxidation of oleic acid with nitric acid,[1] marked a step in the elucidation of the structure of the higher unsaturated fatty acids. It was subsequently obtained by the destructive oxidation of a number of other fatty acids. It is remarkable that adipic acid is the end-product of a considerable number of oxidations ; in 1898 Markownikov [2] observed that the nitric acid oxidation of *cyclo*hexane gave a good yield of adipic acid, and since then the observation has been extended to other *cyclo*hexane derivatives, of which the most easily and cheaply available is *cyclo*hexanol, from the catalytic reduction of phenol. Adipic acid is produced in considerable quantity from this source, and is, with the exception of oxalic, the most readily and cheaply obtainable dibasic acid. It has been used to replace tartaric acid in baking powders, in which it is particularly valuable as its ' raising ' power (ability to form carbon dioxide) is exercised more slowly than with other acidic substances.

Adipic acid forms monoclinic prisms, m. 153° ; it is but moderately soluble in water (1·4 parts per 100 at 15°). It forms an anhydride only with difficulty, Hill having obtained [3] the monomolecular anhydride (125) by the action of

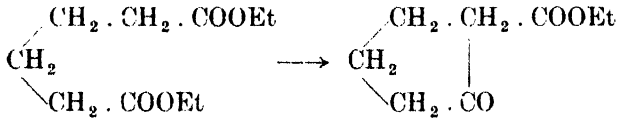


(125)



(126)

acetic anhydride on adipic acid. It is a compound which distils at 98–100° at 0·1 mm. and which solidifies to a crystalline mass at 22°. It can easily be changed by standing or heating to the polymeric forms, which are produced in admixture when attempts are made to dehydrate adipic acid. Distillation of adipic acid in a slow stream of carbon dioxide yields the cyclic ketone, *cyclo*pentanone (126). This, and the formation of analogous cyclic ketones has been discussed in Appendix II of Chapter VI. Adipic ester was shown by Dieckmann[4] to give an internal acetoacetic ester condensation, forming 2-keto*cyclo*pentane carboxylic ester (127).



(127)

Pimelic acid appears to have been prepared first by Dale and Schorlemmer [5] by the oxidation of suberone, previous claims by Laurent having been shown to be due to confusion of mixtures of suberic and adipic acids. The more

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[1] Laurent, *Ann. Chim. Phys.*, 1837, **66**, 154.

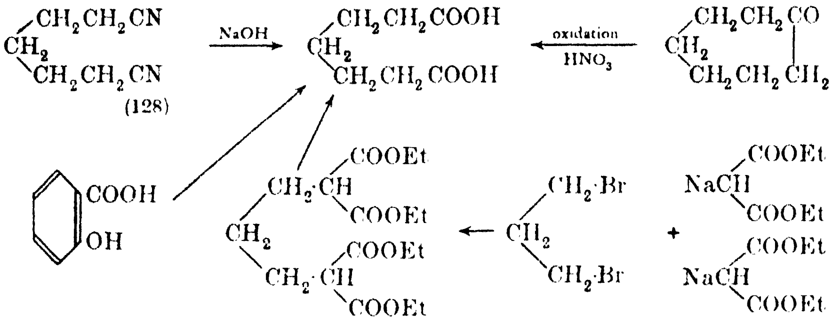
[2] Markownikov, *Ann.*, 1898, **302**, 34.

[3] Hill, *J.A.C.S.*, 1930, **52**, 3470 and 4110.

[4] Dieckmann, *Ann.*, 1901, **317**, 51.

[5] Dale and Schorlemmer, *Ber.*, 1874, **7**, 808 ; *Trans. Chem. Soc.*, 1879, 683.

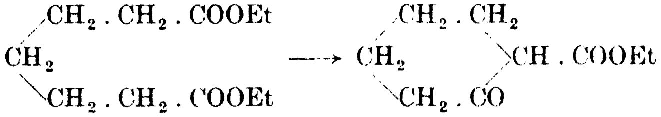
TABLE XVI



common methods of formation of pimelic acid are shown in Table XVI. They are :—

(1) Hydrolysis of the dinitrile (128) obtained by the action of sodium cyanide on an alcoholic solution of pentamethylene dibromide.
(2) The normal malonic ester synthesis from sodio malonic ester and trimethylene dibromide.
(3) By the oxidation of suberone (*cyclo*heptanone).
(4) By the reduction of salicylic acid by sodium and amyl alcohol. This reaction, discovered by Einhorn,[1] is unusual, and offers the most satisfactory method of preparing pimelic acid.

Pimelic acid crystallises in small plates, m. 105·5–106°. Its ethyl ester gives an internal acetoacetic condensation similar to that shown by adipic ester :—



$$\mathrm{CH_2}\begin{cases}\mathrm{CH_2\,.\,CH_2\,.\,COOEt}\\ \mathrm{CH_2\,.\,CH_2\,.\,COOEt}\end{cases} \longrightarrow \mathrm{CH_2}\begin{cases}\mathrm{CH_2\,.\,CH_2}\\ \mathrm{CH_2\,.\,CO}\end{cases}\!\!\!\!>\mathrm{CH\,.\,COOEt}$$

Suberic Acid.—This is one of the longer-known acids of the series having been first prepared by Brugnatelli in 1878 by the oxidation of cork dust.[2] The method is now of historical interest only, although a process has been patented for the production of suberic acid from cork dust using alkaline chlorates in the presence of osmium tetroxide. Industrially the method of Verkade[3] is used for the simultaneous production of suberic and azelaic acids. Commercial ricinoleic acid is added slowly to three times its weight of boiling nitric acid (of d = 1·25) containing a little sodium nitrite. The boiling is continued for five hours and after making up to the original volume with water the oil is separated and the aqueous solution evaporated to dryness. This gives a crude mixture of azelaic and suberic acids weighing about one-fifth of the weight of original ricinoleic acid. The mixture is dissolved in a mixture of benzene and ethanol and the filtered liquid refrigerated. On cooling suberic acid crystallises. The residue from the evaporation of the mother liquors is converted to the magnesium salts when on cooling magnesium azeleate alone separates. The net result is about 11 per cent. of suberic acid and 5 per cent. of azelaic acid, calculated on the ricinoleic acid taken.

When azelaic acid is required in preference to suberic acid, the oxidation is carried out in the cold using acid of density 1·52. The temperature is kept below 10°. After 10 hours the aqueous layer is removed and evaporated and the azelaic acid separated through its magnesium salt. The yield is about 24 per cent. of the weight of ricinoleic acid used.

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[1] Einhorn and Lumsden, *Ann.*, 1895, **286**, 257 ; Müller, *Monatsh.*, 1934, **65**, 18.
[2] Brugnatelli, Crell's *Annalen*, 1787, 145.
[3] Verkade, *Rec. Trav. Chim.*, 1927, **46**, 137.

Suberic acid crystallises in needles, m. 143–144°, azelaic acid in monoclinic plates, m. 107–108°.

By distillation with lime, suberic acid yields the important cyclic ketone, *cyclo*heptanone (see Chap. VI).

Sebacic acid is usually obtained by the distillation of castor oil or ricinoleic acid with potassium hydroxide, or by melting castor oil soap for a period of several hours. On pouring into water and acidifying with hydrochloric acid, sebacic acid separates. It forms leaflets which readily sublime on heating.

The higher acids are of interest mainly on account of their use in preparing cyclic ketones (Chap. VI).

UNSATURATED DIBASIC ACIDS

These acids fall into two classes, those such as fumaric and maleic acids in which the unsaturation lies between the two carboxyl groups and those where unsaturation lies in a side-chain as in ethylidene malonic acid.

The alkylene malonic acids are usually obtained by condensing an aldehyde with malonic ester in the presence of condensing agent such as acetic anhydride, organic bases or sodium ethoxide. The free acids can be obtained, but the esters are more usually required. Some of the members of this series more commonly met with are shown in Table XVII.

TABLE XVII

R. in R—$CH(COOH)_2$	Formula of acid	M.P. of free acid	B.P. diethyl ester
Ethylidene	$CH_3 . CH{=}C(COOH)_2$	82°	117°/17 mm.
Propylidene	$CH_3 . CH_2 . CH{=}C(COOH)_2$	--	115-125°/12 mm.
iso-Propylidene	$(CH_3)_2C{=}C(COOH)_2$	170-171°	110-112°/12 mm.
Butylidene	$CH_3(CH_2)_2CH{=}C(COOH)_2$		144°/25 mm.
Allyl	$CH_2{=}CH . CH_2 . CH(COOH)_2$	102°	222°—
Methyl allyl	$CH_2{=}CH . CH(CH_3)C(COOH)_2$	99°	224°/690 mm.
Ethyl allyl	$CH_2{=}CH . CH(C_2H_5)C(COOH)_2$	107-108°	233°
Propyl allyl	$CH_2{=}CH . CH(C_3H_7)C(COOH)_2$	115°	240-241°
Butyl allyl	$CH_2{=}CH . CH(C_4H_9)C(COOH)_2$	—	130°/10 mm.
Undecenyl	$CH{=}CH(CH_2)_9CH(COOH)_2$	112-113°	154°/2 mm.
Docosenyl	$CH_3(CH_2)_7CH{=}CH(CH_2)_{12}CH(COOH)_2$	--	270°/1 mm.

The dibasic acids in which the unsaturation is in the main stem constitute a very important group of substances amongst which are found some of the simplest and most characteristic examples of geometrical isomerism. In Table XVIII are given the names and physical properties of the members of this group more commonly met with. Throughout this section the terms "*cis*" and "*trans*" denote the positions of the two carboxyl groups.

Maleic and Fumaric Acids.—Lassaigne[1] in 1818 drew attention to the fact that the sublimate from heated malic acid (previously commented upon by Vauquelin[2] and Braconnot[3]) was a new acid, distinct from the acid isolated from the aqueous distillate during the same experiments. The aqueous solution yielded a very soluble acid which Lassaigne called 'paramalic' acid. The name 'maleic' was given to it by Pelouze in 1834; he called the sublimed acid

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[1] Lassaigne, *Ann. Chim. Phys.*, 1818, [2], **9**, 93.

[2] Vauquelin, *ibid.*, 1817, [2], **6**, 337.

[3] Braconnot, *ibid.*, 1818, [2], **8**, 149.

TABLE XVIII

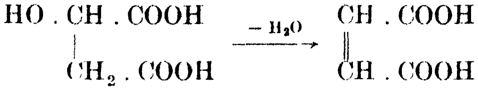
Systematic name	Common name	M.P.	Dissociation constants	
			$K_1 \times 10^4$	$K_1 \times 10^5$
cis-Butene-2-diacid	Maleic	130–131°	130	300–800
trans-Butene-2-diacid	Fumaric	286–287° (sealed tube)	9	3·5
cis-2-Methyl-butene-2-diacid	Citraconic	91°	34	0·05
trans-2-Methyl-butene-2-diacid	Mesaconic	205°	8	0·7
2-Methylbutene diacid	Itaconic	161°	1·5	0·25
cis-Pentene-2-diacid	*cis*-Glutaconic acid	136°	1·5	—
trans-Pentene-2-diacid	*trans*-Glutaconic acid	138°	1·8	0·84
cis-Hexene-2-diacid	*cis*-α-Dihydromuconic acid	81°	—	—
trans-Hexene-2-diacid	*trans*-α-Dihydromuconic acid	198°	—	—
Hexene-3-diacid	β-Dihydromuconic acid	195°	—	—
trans-trans-Hexadiene-2, 4, diacid	*trans*-Muconic acid	298°	—	—
cis-cis-Hexadiene-2, 4, diacid	*cis*-Muconic acid	187°	—	—
cis-cis-3-Methylhexadiene-2, 4, diacid	*cis*-β-Methylmuconic acid	171°	—	—
trans-trans-3-Methylhexadiene-2, 4 diacid	*trans*-β-Methylmuconic acid	235°	—	—
cis-cis-Heptadiene-2, 4, diacid	Piperylenedicarboxylic acid	169°	—	—
trans-trans-Octadiene-3, 5, diacid	—	260°	—	—
Decatetraene-2, 4, 6, 8, diacid	$HOOC\,.\,(CH{=}CH)_4COOH$	309°	chrome yellow crystals	
2, 5, 9, Trimethyldecatetraene-2, 4, 6, 8 diacid	$HOOC\,.\,C(CH_3){=}CH\,.\,CH{=}C(CH_3)$ $HOOC\,.\,C(CH_3){=}CH\,.\,CH{=}CH$	296°	yellow crystals	

'paramaleic acid'. It had, however, been previously obtained and examined under different names, e.g.,

- 'boletic acid' from lichens and fungi (Braconnot),
- 'lichenic acid' from Iceland Moss (Pfaff),
- 'fumaric acid' from fumitory (*Fumaria officinalis*) (Winkler).

It was demonstrated that the paramaleic, boletic and lichenic acids are identical with fumaric acid, and the latter name has been adopted. The foregoing remarks have already indicated that fumaric acid is fairly widely distributed naturally; maleic acid is seldom, if ever, found naturally.

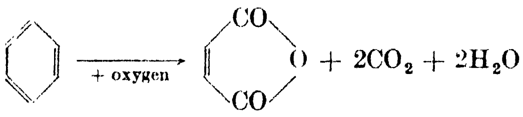
Maleic acid can be obtained by the method indicated in the previous paragraph, namely, by the prolonged action of heat on malic acid :—



$$\begin{array}{l}HO.CH.COOH\\ |\\ CH_2.COOH\end{array} \xrightarrow{-H_2O} \begin{array}{l}CH.COOH\\ \|\\ CH.COOH\end{array}$$

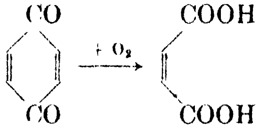
the yield is low, much fumaric acid being simultaneously formed. If, however, acetyl chloride and malic acid are warmed together on the water-bath, hydrogen chloride is evolved and a mixed acetyl-malic anhydride is formed which on distillation yields maleic anhydride in good yield. The anhydride, mixed with the theoretical amount of water and seeded with a crystal of maleic acid gives the required acid in good yield.

The production of large quantities of maleic acid has been made possible by the use of processes involving the catalytic oxidation of benzene at moderately high temperatures in the presence of vanadium oxides. The reaction proceeds to a large extent according to the equation :—



Maleic acid and its anhydride, are thus, industrially available, although the process is difficult to control and the product hard to obtain pure. It was thought that maleic acid, or malic acid prepared from it, might replace the citric and tartaric acids so widely used in the foodstuffs and beverage industries. This has not proved feasible, since maleic acid itself has a disagreeable flavour.

The oxidation of aromatic compounds, chemically, to maleic acid is not uncommon ; and when quinone is oxidised by 'silver peroxide '[1] up to 70 per cent. of the theoretical amount of maleic acid is obtained.

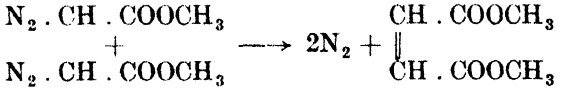


In addition, maleic acid can be obtained by a variety of synthetic reactions, of which a few are outlined below :—

(1) Glyoxylic acid and malonic acid condense to give maleic and fumaric acids :—[2]

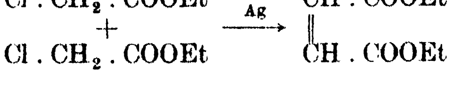
$$HOOC.CHO + CH_2(COOH)_2 \longrightarrow HOOC.CH{=}C(COOH)_2$$
$$\longrightarrow HOOC.CH{=}CH.COOH + CO_2$$

(2) The spontaneous decomposition of diazoacetic ester also yields esters of the two acids :—[3]



$$\begin{array}{c}N_2.CH.COOCH_3\\ +\\ N_2.CH.COOCH_3\end{array} \longrightarrow 2N_2 + \begin{array}{l}CH.COOCH_3\\ \|\\ CH.COOCH_3\end{array}$$

(3) Silver powder reacts upon ethyl chloracetate to give maleic ester :—[4]



$$\begin{array}{c}Cl.CH_2.COOEt\\ +\\ Cl.CH_2.COOEt\end{array} \xrightarrow{Ag} \begin{array}{l}CH.COOEt\\ \|\\ CH.COOEt\end{array}$$

---

[1] Silver peroxide is only present in the reaction mixture in limited quantities ; a solution of silver sulphate in sulphuric acid is mixed with potassium persulphate and the mixture neutralised (cf. Kempf, *Ber.*, 1906, **39**, 3722).

[2] Döbner, *ibid.*, 1901, **34**, 53.

[3] Loose, *J. Pr. Chem.*, 1909, **79**, 508.

[4] Tanatar, *Ber.*, 1879, **12**, 1563.

Fumaric acid can be obtained readily from maleic acid ; or in quite good yield (up to 70 per cent.) by the fermentation of sucrose by *Aspergillus fumaricus*.[1] It may also be prepared by heating bromosuccinic acid with water or bases such as pyridine.

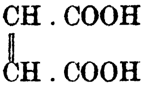
The gradual transformation of maleic acid to fumaric acid takes place at ordinary temperatures and in solution, and is greatly accelerated by ultra-violet irradiation or by the presence of catalysts, of which bromine is commonly used, although many others (platinum, halogen acids, thiocyanates) are known.

The reverse process—fumaric to maleic, can be accomplished by the ultra-violet or radium irradiation of alcoholic solutions of fumaric acid. Irradiation of various mixtures of maleic and fumaric acid in alcohol show that an equilibrium is reached in this solvent with 72 per cent. of maleic and 28 per cent. of fumaric acid. An indirect conversion of fumaric into maleic acid is obtained by strongly heating the former when maleic anhydride is obtained ; this readily combines with water to give maleic acid. The properties of the two acids are contrasted in Table XIX.

TABLE XIX

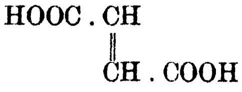
	Maleic acid	Fumaric acid
Form	Rhombic prisms	Polymorphic, mainly in prisms
M.P.	130·130·5°	286-287° (sealed tube)
Solubility in water	Considerable 32·6 g./in 100 g. of soln. at 10° 75 g./in 100 g. of soln. at 80°	Slight 0·3 per 100 c.c. at 10°
Taste	Acid ; followed by disagreeable nauseous taste	Pure acid
Dimethyl ester	b. 205°	m. 102° ; b. 192°
Monomethyl ester	—	m. 144·5°
Diethyl ester	b. 225°	m. 0·5° ; b. 218°
Monoethyl ester	Syrup	m. 70° ; b. 147°/16 mm.
Anhydride	M.p. 52-53°. Prisms	—

The assignment of the formulæ, indicated below, to maleic and fumaric acid respectively depends on the following facts, although the force of (3) is vitiated by the possibility of *trans*- addition :—



$$\begin{array}{l} \mathrm{CH\,.\,COOH} \\ \| \\ \mathrm{CH\,.\,COOH} \end{array}$$

Maleic acid



$$\begin{array}{r} \mathrm{HOOC\,.\,CH} \\ \| \quad\quad\quad\; \\ \mathrm{CH\,.\,COOH} \end{array}$$

Fumaric acid

(1) The formation of maleic and not fumaric acid by the direct oxidation of quinone points to a *cis*-configuration.

(2) The formation of an anhydride from maleic acid alone is compatible only with *cis*- structures. (This is particularly evident from an examination of the atomic models for these two acids.)

(3) Oxidation by permanganate of either maleic or fumaric acid yields a tartaric acid—mesotartaric acid from maleic acid and racemic tartaric acid from fumaric acid. These transformations are shown in the formulæ at top of next page, and can be followed more easily by the use of atomic models. The inter-conversion of maleic acid and fumaric acid, and the reactions of the halogenated derivatives of these acids, involves a detailed consideration of stereochemical principles and is deferred to Chapter IV, Vol. III.

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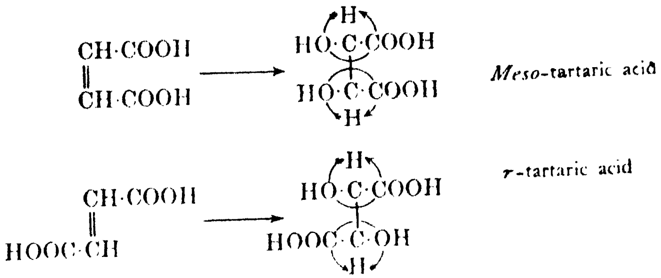
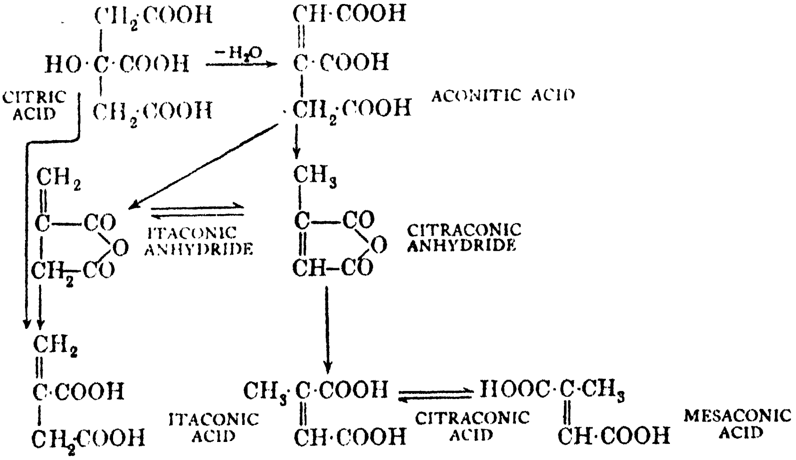
[1] Wehmer, *Ber.*, 1918, **51**, 1663.



Citraconic, Mesaconic and Itaconic Acids.—The dry distillation of citric acid by Lassaigne in 1822 led to the discovery of citraconic acid [1] which was named 'pyrocitric' acid by Lassaigne. In 1836, Baup [2] isolated from the distillate a second acid, and a third from the residue remaining in the retort. These he named as follows :—

Lassaigne	*Baup's Acids*	*Modern Nomenclature*
Pyrocitrique	Citribique	Citraconic acid
	Citricique	Itaconic acid
	Citridique	Aconitic acid (Equisetic acid)

It will be noted that mesaconic acid does not occur in this group of names, being subsequently discovered and named by Gottlieb in 1851,[3] by boiling aqueous solutions of citraconic acid with dilute nitric acid. The relation of these substances is given in the scheme below :—



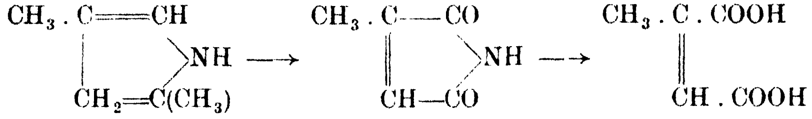
These acids are not all of natural occurrence ; citric acid is, of course, widely distributed in natural fruit juices, whilst aconitic acid is widely distributed in various aconites, and in many of the *Equisetaceæ*—thus giving rise to its obsolete name 'equisetic acid', given by Braconnot in 1828. The other acids have scarcely ever been recorded in natural products, with the exception of the occurrence of mesaconic acid in cabbage.[4]

The preparation of citraconic acid is usually carried out by the rapid distillation of citric acid, which yields a liquid distillate composed of itaconic and citraconic anhydrides. On rectification at ordinary pressure the itaconic anhydride isomerises to citraconic anhydride, which distils in a tolerably pure form. Treated with the theoretical amount of water and cooled in an ice-box, citraconic acid is formed as a mass of crystals. The conversion of citraconic to mesaconic acid is very easily accomplished by irradiating a chloroform solution of citraconic acid to which a trace of bromine has been added. Crystals of mesaconic acid rapidly separate.

---

[1] Lassaigne, *Ann. Chim. Phys.*, 1822, **21**, 100.
[2] Baup, *Ann.*, 1836, **19**, 29 ; 1839, **29**, 169.
[3] Gottlieb, *ibid.*, 1851, **77**, 268.
[4] Buston, *Biochem. J.*, 1928, **22**, 1523.

Constitutionally, the formation of citraconic acid through its imide by the oxidation of 2, 4-dimethylpyrrole with chromic acid[1] is strong evidence for



the *cis*- formula normally accorded to it. In general, it is found that a species of equilibrium exists between itaconic, citraconic and mesaconic acids, which exist together in the proportions 1 : 1 : 4. This equilibrium is redistributed by certain catalysts, such for example, as mercuric chloride, potassium persulphate which converts citraconic acid to itaconic acid almost quantitatively.[2] It may be added that in distinguishing between *cis*- and *trans*- isomers of the maleic-fumaric group, consideration of the dipole moment (see also Chap. VII, Vol. III) is of great value. Since the possession of a dipole moment depends on the non-identity in space of the proton and electron centres of the molecule, this will be much larger in the case of *cis*- than of *trans*- compounds. Thus, in many simple cases the *cis*- isomer has a positive dipole moment, whilst that of the *trans*- isomer is zero, e.g.,

	$\mu \times 10^{18}$
cis-Dibromethylene	1·22
trans-Dibromethylene	0
cis-Diethyl maleate	2·54
cis-Diethyl fumarate	2·38

The difference is not so marked in more complex instances, e.g., the maleic and fumaric esters, but is usually sufficient to distinguish the two isomers.

Numerous alkyl derivatives of maleic and citraconic acids are known, many of which have been obtained from oxidative degradation of the pyrrole fragments of blood and plant pigments. Some of these are listed in Table XX.

Glutaconic acid, $HOOC . CH{=}CH . CH_2 . COOH$, the derivatives of which have given rise to extensive researches into three-carbon tautomerism, does not appear to occur naturally. It was first prepared by Conrad and Gutzeit in 1883 by the action of chloroform on sodio-malonic ester :—

$$\begin{array}{l} (EtOOC)_2CHNa + CHCl_3 + NaCH(COOEt)_2 \\ \qquad\qquad \longrightarrow (EtOOC)_2C{=}CH . CH(COOEt)_2 \\ \qquad\qquad\qquad\qquad \downarrow \\ \qquad\qquad\qquad HOOC . CH{=}CH . CH_2 . COOH \end{array}$$

It can also be obtained by dehydration of the compound formed by the reduction of acetone dicarboxylic acid :—

$$\begin{array}{l} HOOC . CH_2 . CO . CH_2 . COOH \\ \downarrow \\ HOOC . CH_2 . CH(OH)CH_2 . COOH \\ \downarrow \\ HOOC . CH_2 . CH{=}CH . COOH \end{array}$$

---

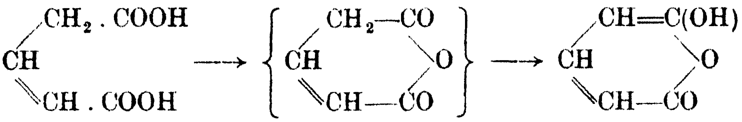
[1] Plancher and Cattadori, *Gazz. Chim. Ital.*, 1903, **331**, 405.

[2] Wieland and Zilg, *Ann.*, 1937, **530**, 273.

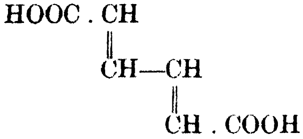
TABLE XX

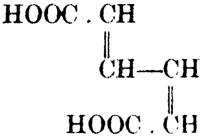
Names		Formulæ	M.	
Ethyl maleic	**(Homocitraconic)**	$C_2H_5 . C(COOH)=CH . COOH$	101°	Remarkable for rapid conversion to methyl itaconic acid.
Ethyl fumaric	**(Homomesaconic)**		195°	
Dimethyl maleic	**Pyrocinchoninic acid**	$CH_3 . C(COOH)=C(CH_3)COOH$	—	Pyrocinchoninic anhydride is made by the unusual action of heat on ethylene tetracarboxylic acid.
Dimethyl fumaric	—		240°	
Propyl maleic	**(γ-ethyl citraconic)**	$C_3H_7 . C(COOH)=CH . COOH$	93°	
	(γ-ethyl mesaconic)		175°	
***iso*-Butyl maleic**		$(CH_3)_2CH . CH_2 . C(COOH)=CH . COOH$	78°	
***iso*-Butyl fumaric**			185°	
Diethyl maleic	**Xeronic acid**	$C_2H_5 . C(COOH)=C(C_2H_5)COOH$		A by-product in the formation of citraconic anhydride.
***n*-Heptyl maleic**		$C_7H_{15} . C(COOH)=CH . COOH$	86°	
***n*-Heptyl fumaric**			154°	

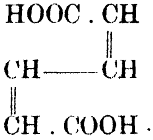
Glutaconic acid prepared in this way crystallises in prisms, m. 136–138° and is most probably the *trans-* form, although it forms an anhydride on digestion with acetic anhydride. This anhydride has an unusual structure, and behaves as a monobasic acid (128a).


(128a)

Muconic acid, HOOC . CH=CH . CH=CH . COOH, with two ethylenic bonds in its stem should be capable of existence in three forms :—


trans-trans


cis-trans


cis-cis

Of these, two are known with certainty, the *cis-cis* form, m. 187°, and a form, m. 298°, which appears to be the *trans-trans* form. Böeseken and Sloof[1] have isolated what may be the third form by the oxidation of *o*-quinone. Muconic acid is one end-point of the biological disposal of benzene, and although its formation in this way has been amply confirmed, the transformation has not been achieved by purely chemical means. Muconic acid can be obtained by the condensation of glyoxal with malonic acid in pyridine :—

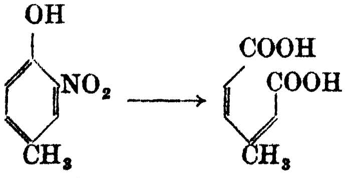
$$\begin{array}{l} (HOOC)_2CH_2 + OCH.CHO + CH_2(COOH)_2 \\ \downarrow \\ (HOOC)_2CH{=}CH.CH{=}CH(COOH)_2 \\ \downarrow \\ HOOC.CH{=}CH.CH{=}CH.COOH \end{array}$$

The method gives a poor yield, but is of constitutional significance. Muconic acid forms minute needles, almost insoluble in cold water. It readily undergoes reduction by sodium amalgam giving the symmetrical dihydro- compound by 1 : 4-addition :—

$$\begin{array}{ll} & HOOC.CH{=}CH.CH{=}CH.COOH \\ & \downarrow \text{NaHg} \\ (129) & HOOC.CH_2.CH{=}CH.CH_2.COOH \\ & \downarrow \text{Heat} \\ (130) & HOOC.CH{=}CH.CH_2.CH_2.COOH \end{array}$$

The symmetrical dihydromuconic acid (129) obtained by reduction of muconic acid is a labile form, m. 195°. On heating it rapidly passes into a mixture of the *cis-* and *trans-* forms of the $\alpha\beta$ unsaturated acid (130), m. 81° and 195° respectively.

β-Methyl muconic acid (132) is interesting[2] as being formed by the oxidation of 3-nitro-4-hydroxytoluene (nitro-*p*-cresol) (131) :—


(131) (132)

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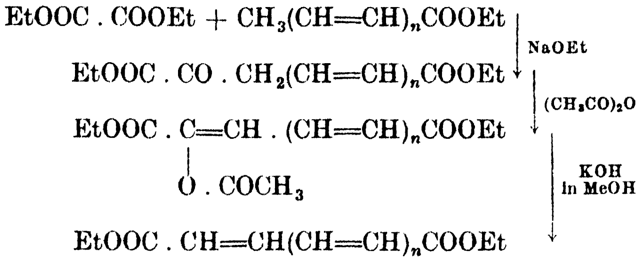
[1] Böeseken and Sloof, *Proc. Acad. Sci. Amsterdam*, 1929, **32**, 1043.

[2] Pauly, Gilmour and Will, *Ann.*, 1918, **416**, 14.

Some of the higher unsaturated acids of this series, e.g., crocetin belong to the family of polyene plant pigments and are discussed in Chapter XI. In this connexion it is interesting to note that Kühn[1] has prepared a long series of polyene-αω-diacids by the generic reaction :—

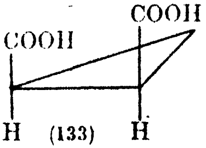


$$EtOOC\,.\,COOEt + CH_3(CH{=}CH)_nCOOEt \xrightarrow{NaOEt} EtOOC\,.\,CO\,.\,CH_2(CH{=}CH)_nCOOEt \xrightarrow{(CH_3CO)_2O} EtOOC\,.\,\underset{O\,.\,COCH_3}{C}{=}CH\,.\,(CH{=}CH)_nCOOEt \xrightarrow[\text{in MeOH}]{KOH} EtOOC\,.\,CH{=}CH(CH{=}CH)_nCOOEt$$

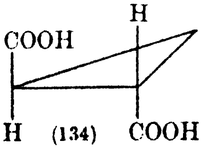
Where $n = 3$, decanetetraene-2, 4, 6, 8 diacid-1, 10 is obtained as vivid chrome yellow crystals, m. 309°. The next homologue, dodecanepentaene-2, 4, 6, 8, 10 diacid-1, 12 has similar properties.

CYCLIC DICARBOXYLIC ACIDS

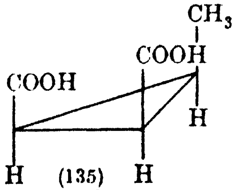
*Cyclo*propane dicarboxylic acids are, by virtue of their ring-structure, capable of *cis-trans-* isomerism (133 and 134). When a third (or differing third and fourth) substituent is attached to the third carbon atom of the ring an additional form occurs ; these configurations are shown in formulæ (135) to (137). An additional type of *cyclo*propane dicarboxylic acid is that carrying two carboxyls on the same carbon atom (138). A careful examination of the *trans-* dicarboxylic acid structure (134), will show that it cannot be superposed on its mirror-image ; it should, therefore, be capable of optical isomerism. The resolution by Buchner of this acid into its *dextro-* and *lævo-* forms, *via* the brucine salts is a strong additional proof of the validity of the general arguments on which rests the assignment of *cis-* and *trans-* structures. The main examples of this group are listed in Table XXI on page 548.



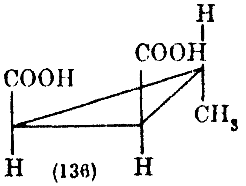
(133)
cis-



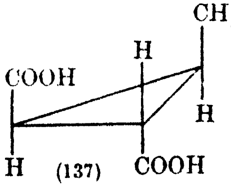
(134)
trans-



(135)
cis-I-



(136)
cis-II-



(137)
trans-

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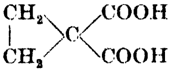
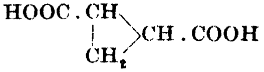
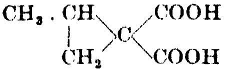
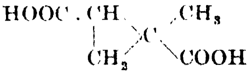
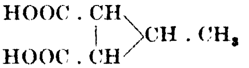
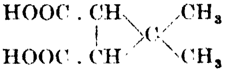
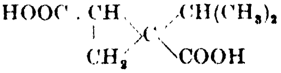
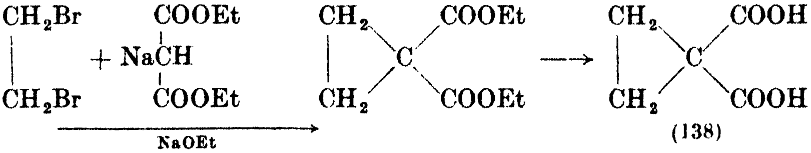
[1] Kühn and Grundmann, *Ber.*, 1936, **69B**, 1757 ; 1979.

TABLE XXI

Name	Formula	M.P.
*cyclo*Propane 1, 1 dicarboxylic acid (Vinaconic acid)		140-141°
*cyclo*Propane 1, 2 dicarboxylic acid	 *cis-* *trans-*	139° 175°
1-Methyl*cyclo*propane 2, 2 dicarboxylic acid	 (138)	113·5°
1-Methyl*cyclo*propane 1, 2 dicarboxylic acid	 *cis-* *trans-*	142° 168°
1-Methyl*cyclo*propane 2, 3 dicarboxylic acid	 *cis-I-* *cis-II-* *trans-*	108° 147° 195°
1, 1-Dimethyl*cyclo*propane 2, 3 dicarboxylic acid (Caronic acid)	 *cis-* *trans-*	186° 213°
1-*iso*-Propyl*cyclo*propane 1, 2 dicarboxylic acid (Umbellularic acid)		120-121°

Some of the above compounds, e.g., caronic and umbellularic acids, are the results of oxidative degradation carried out on natural substances and, as such, are invaluable in the elucidation of structure. General methods for the synthesis of *cyclo*propane dicarboxylic acids are not dissimilar to those used for the monocarboxylic acids (see p. 507); the more important are listed below :—

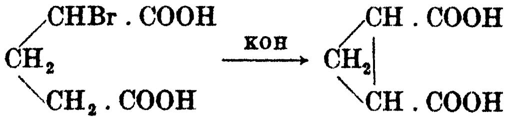
(1) The condensation of ethylene dibromide or its substituted derivatives, with sodiomalonic ester in the presence of excess sodium ethoxide yields *cyclo*propane 1, 1 dicarboxylic ester or its derivatives :—



(138)

from which the acids themselves can be obtained by cautious hydrolysis. They act as true malonic derivatives giving the corresponding monocarboxylic compounds on heating.

(2) The simple 1, 2 dicarboxylic acids may be obtained quite easily from α-bromoglutaric acid or its derivatives by the action of potash.



β-Substitution favours the reaction, which in the hands of Ingold[1] proved a valuable weapon in unravelling the problems of three-carbon tautomerism.

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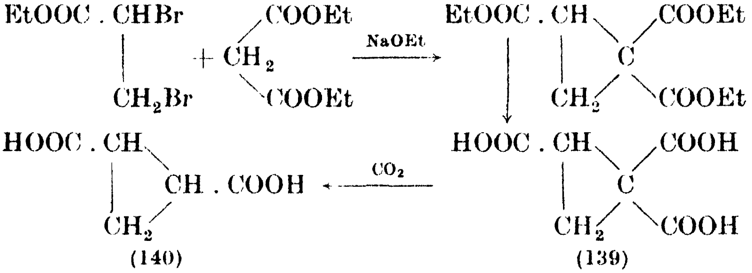
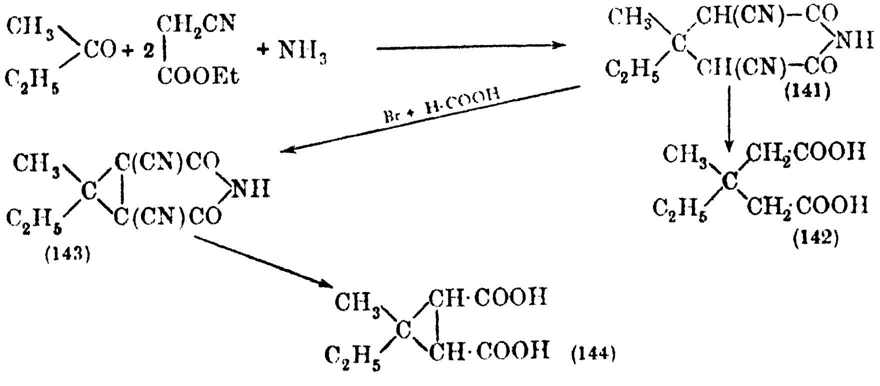
[1] Ingold, *J.C.S.*, 1921, **119**, 305 ; 1922, **121**, 2676 ; 1925, **127**, 387.

(3) Probably the most accessible route to the 1, 2 dicarboxylic acids for preparative purposes is through the tricarboxylic acid which is obtained in good yield from $\alpha\beta$ dibromopropionic ester, malonic ester and sodium ethoxide



By heating the tricarboxylic acid (139) to 200°, or by prolonged boiling with acetic anhydride, the anhydride of the *cis-* form of the dicarboxylic acid is formed—a solid, m. 59° (140). Treatment of the molten anhydride with the theoretical quantity of water gives the *cis-* acid itself. The *cyclo*propane ring makes isomerisation of *cis-* to *trans-* acid more difficult than with acids such as citraconic ; thus, a short heating at 240° with potassium hydroxide is necessary.

(4) *The Guareschi reaction* can be applied to the preparation of *cyclo*propane dicarboxylic acids. Thus, when a ketone reacts in the presence of ammonia, with cyanacetic ester, a cyclic imide (141) is produced which on hydrolysis gives a disubstituted[1] glutaric acid[2] (142). The cyclic imide has two 'active' groups and will react through its sodio derivative with further alkyl halide molecules, giving tetrasubstituted glutaric acids ; on the other hand, when treated with bromine and formic acid, by the method of Birch, Gough and Kon,[3] they yield the bicyclic imides of the *cyclo*propane-dicarboxylic acids (143), from which the latter (144) may be obtained by hydrolysis.



(5) Substituted *cyclo*-propane dicarboxylic acids are formed directly by the dehydrating action of thionyl chloride on the esters of tri-substituted malic acids,[4] or on paraconic acids :—[5]

---

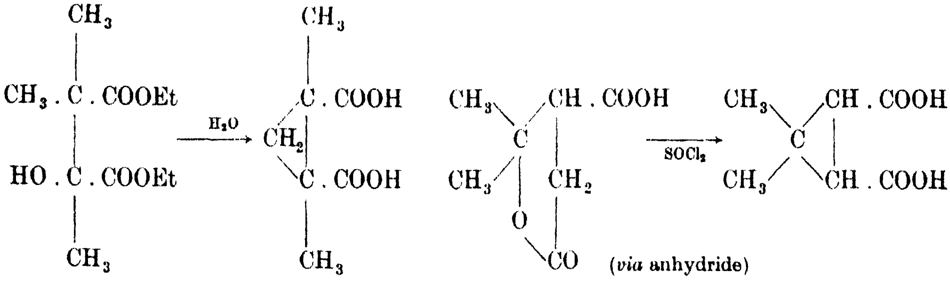
[1] Guareschi, *Zent.*, 1901, I, 571 and 821.

[2] Kon and Thorpe, *J.C.S.*, 1919, **115**, 686.

[3] Birch, Gough and Kon, *ibid.*, 1921, **119**, 1315.

[4] Auwers and Ungemach, *Ann.*, 1934, **511**, 152.

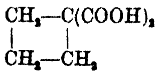
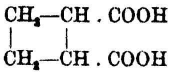
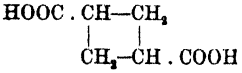
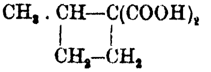
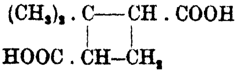
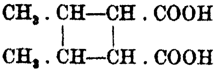
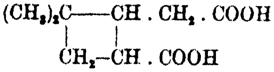
[5] Barbier and Locquin, *C.R.*, 1911, **153**, 188.



*cyclo*Butane Dicarboxylic Acids

This group of compounds is by no means so well represented as are the corresponding *cyclo*propane derivatives, but the few compounds which are known have an important relation to terpene chemistry, being frequently produced during the degradative oxidation of members of the pinene group. The commonest members of the series are shown in Table XXII.

TABLE XXII

Name	Formula	M.P.
*cyclo*Butane 1, 1 dicarboxylic acid		158°
*cyclo*Butane 1, 2 dicarboxylic acid		*cis*- 139° *trans*- *d* or *l*, 105°, *rac*. 131°
*cyclo*Butane 1, 3 dicarboxylic acid		*cis*- 155° *trans*- 170°
1-Methyl*cyclo*butane 2, 2 dicarboxylic acid		158°
1, 1-Dimethyl*cyclo*butane 2, 4-dicarboxylic acid		*cis*- 176° *trans*- 146° Norpinic acid
1, 2-Dimethyl*cyclo*butane 3, 4-dicarboxylic acid		*cis*- 88° *trans*- 201°
1, 1-Dimethyl-3-carboxy-2-*cyclo*butyl acetic acid		*rac*. 101–102° Pinic acid *d* or *l* 135° Caryophyllenic acid

The methods by which these compounds are synthesised are entirely analogous to those already described in connexion with the *cyclo*propane derivatives. The Guareschi method with methylene di-iodide is one of the most successful for symmetrical acids such as norpinic acid.[1]

The stereochemical problems of *cyclo*butane dicarboxylic acids have attracted research workers for the last thirty years. There are five stereochemical structures to be derived from a *cyclo*butane nucleus carrying four substituents, two each of two different kinds alternating, as set out in the scheme below :—

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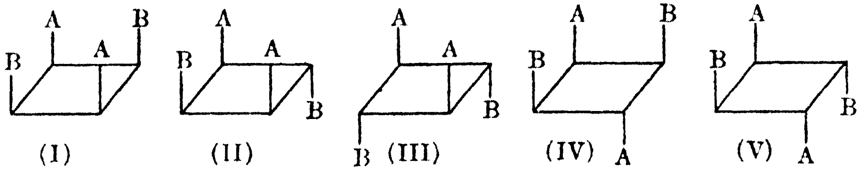
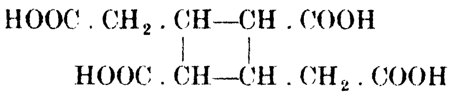
[1] Kerr, *J.A.C.S.*, 1929, **51**, 614.



Ingold, in 1922,[1] made a survey of the five acids in which A = COOH and B = CH_2 . COOH and obtained evidence of the structure of all five :—

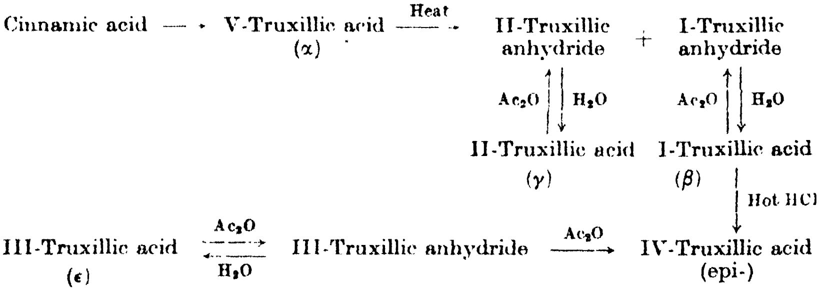


$$\begin{array}{l} HOOC\,.\,CH_2\,.\,CH{-}CH\,.\,COOH \\ \qquad\qquad\quad |\qquad | \\ \quad HOOC\,.\,CH{-}CH\,.\,CH_2\,.\,COOH \end{array}$$

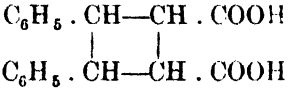
	M.P.
α = V	234°
β = I	198°
γ = II	186°
δ = IV	207°
ε = III	223°

An entirely similar problem exists with the five truxillic acids[2] which can all be obtained from the α-acid (V. A = COOH, B = C_6H_5). α-Truxillic acid is obtained by the dimerisation of cinnamic acid (q.v.) and the five forms correspond to the five structures given above. Their interconversion is indicated in the following scheme :—

TABLE XXIII



The acids are sometimes distinguished by the Greek letters set out in brackets after their names above. The II and IV acids give half-anilides (one —COOH converted to —CO . NH . C_6H_5) which can be resolved into optically active forms ; the half-anilides of the other three forms are not resolvable. This is at one and the same time a confirmation of the *cyclo*butane structure of the truxillic acids, and of the correctness of the assignment of the structures (145) to the five acids. These five acids must not be confused with the ten structurally isomeric truxinic acids of the form :—



$$\begin{array}{l} C_6H_5\,.\,CH{-}CH\,.\,COOH \\ \qquad\quad |\qquad | \\ C_6H_5\,.\,CH{-}CH\,.\,COOH \end{array}$$

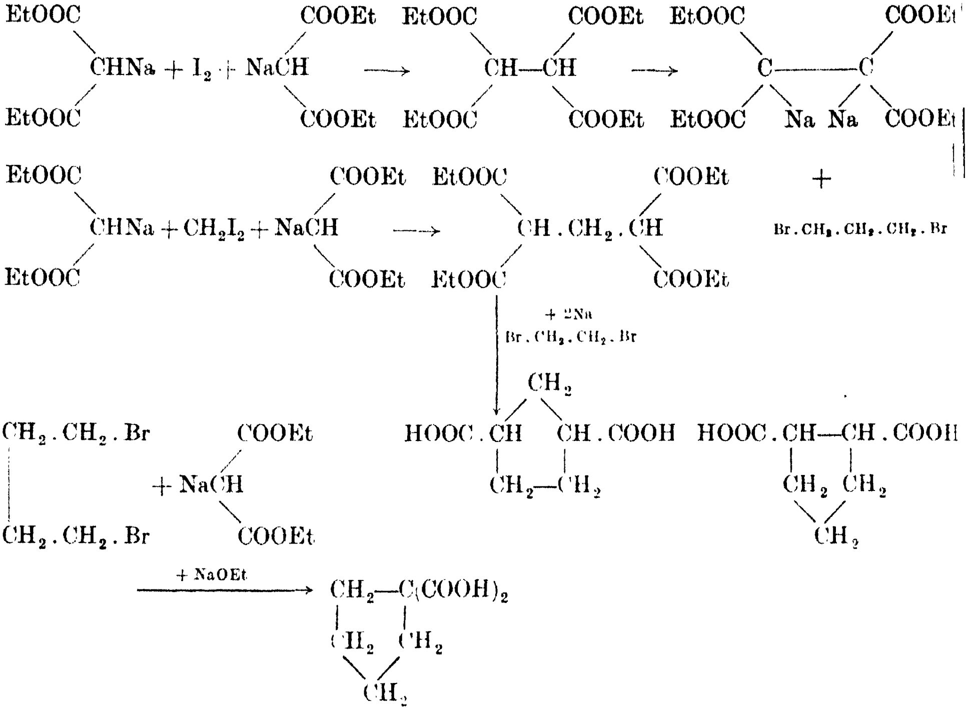
CYCLOPENTANE DICARBOXYLIC ACIDS

Dicarboxylic acids of this group are obtained either by a malonic or Guareschi synthesis, or by the oxidation of naturally occurring cyclic substances—such as the camphors in which the pentacyclic ring is preformed. The diagram below gives an indication of some of the reactions available.

---

[1] Ingold, Perren and Thorpe, *J.C.S.*, 1922, **121**, 1784, 1765.

[2] Stobbe and Zschoch, *Ber.*, 1923, **56B**, 576 ; Stoermer and Bacher, *Ber.*, 1924, **57B**, 15.



Some properties of the acids of this series are recorded in Table XXIV.

TABLE XXIV

SOME *CYCLO*PENTANE DICARBOXYLIC ACIDS

Substituents in the *cyclo*pentane ring					Special name	M.P.
1	2	3	4	5		
$(COOH)_2$	—	—	—	—		185°
COOH	COOH	—	—	—	*cis*- *trans*- *d* or *l* *trans*- *rac.*	140° 181° 163°
COOH	—	COOH	—	—	*cis*- *trans*- *d* or *l* *trans*- *rac*-	121° 93° 88°
$(COOH)_2$	CH_3	—	—	—		174°
$(COOH)_2$	—	CH_3	—	—		141°
COOH	COOH	CH_3	—	—		104°
$\{CH_2COOH$ $COOH\}$	—	—	—	—		156·5°
COOH	—	CH_2COOH	—	—	Homonorcamphoric acid	137°
COOH	CH_3	(CH_3) $(COOH)$	—	—	Santonic acid	171°
COOH	$(CH_3)_2$	(CH_3) $(COOH)$	—	—	Camphoric acid *cis*- *d* and *l* Camphoric acid *trans*- *d* and *l*	187° 171°
COOH	$(CH_3)_2$	COOH	—	—	Apocamphoric acid	

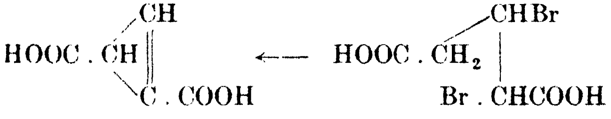
Of the *cyclo*hexane dicarboxylic acids, the hexahydrophthalic acids are of considerable importance, both structurally and synthetically. The three acids have the following properties :—

	M.P. *cis*- form		M.P. *trans*- form
Hexahydrophthalic acid . . .	192°		215° rac. ; 179-183°, *d* or *l*
Hexahydro*iso*phthalic acid . .	163°		148°
Hexahydro*tere*phahalic acid . .	167°		309°
*Cyclo*hexane 1, 1-dicarboxylic acid .	—	207°	—

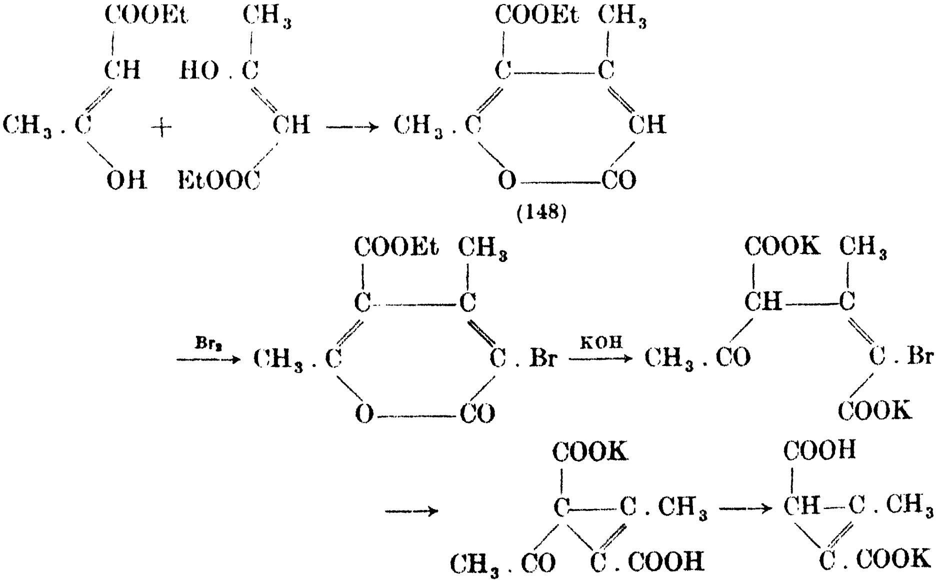
In the case of the *cis*- acids of the *ortho*- and *meta*- dicarboxylic acids, no optical activity is observable as the compounds are internally compensated. On the other hand, the *trans*- isomers of these acids are capable of resolution into two optically active isomers ; neither *trans*- nor *cis*- hexahydro*tere*phthalic acids give rise to optical activity as they both have a plane of symmetry. Another unusual feature of these acids is that both *cis*- and *trans*-hexahydrophthalic acids give an anhydride.

UNSATURATED ALICYCLIC DICARBOXYLIC ACIDS

A few *cyclo*-propene dicarboxylic acids are known, and prove to be of some interest ; the simplest, *cyclo*-propene-1, dicarboxylic acid-1, 3 (146) is prepared


(146) (147)

by the action[1] of caustic potash on αβ-dibromoglutaric acid (147). The 2-methyl derivative of this acid—2-methyl*cyclo*-propene-1, dicarboxylic acid-1, 3—is extremely interesting in relation to the theories of three-carbon tautomerism. When acetoacetic ester polymerises, some *iso*-dehydroacetic acid (148)


(148)

(149)

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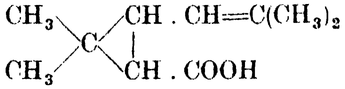
[1] Farmer and Ingold, *J.C.S.*, 1921, **119**, 2015.

is formed ; this, if brominated and treated with caustic alkali, yields the methyl*cyclo*propene dicarboxylic acid (149) by a series of changes which probably take the course indicated above. Several series of isomers of this acid have been reported, but have proved on investigation not to have a cyclic structure. Thus, Kon and Nanji[1] showed that the alleged labile ester was really the ester of hexyne-2, diacid-1, 6, $HOOC . C{\equiv}C . CH_2 . CH_2 . COOH$. There appear, therefore, to be no geometrical isomers of this acid, although, of course, it can, by virtue of its single asymmetric carbon atom, be resolved into *d*- and *l*-forms.

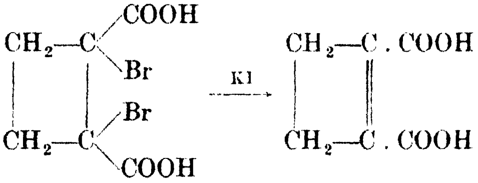
Mention may be made appropriately at this point of chrysanthemum dicarboxylic acid, which, although not a *cyclo*propene derivative, is closely related to the unsaturated acids of this group. It has the constitution[2] (150)



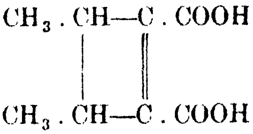
(150)

and occurs naturally in pyrethrum.

Until recently only one *cyclo*-butene dicarboxylic acid (151) was known ; it can be obtained as a crystalline substance, m. 178°, by the action of potassium



(152) (151)



(153)

iodide[3] on dibromo*cyclo*butane dicarboxylic acid (152). Recently, another acid of this series (153), the dimethyl analogue of the former, has been discovered as a breakdown product from caryophyllene ; it is called 'dehydronorcaryophyllenic acid '.[4]

Few of the acids of the *cyclo*pentene, *cyclo*hexene and *cyclo*hexadiene groups, other than the reduced phthalic acids, are of outstanding interest. On the other hand, the partially reduced phthalic acids are of particular interest on account of their contributions to the study of aromatic character. Mention has been made of the fully hydrogenated hexahydrophthalic acids, the properties of which are frankly alicyclic ; on the other hand, the phthalic acids themselves are definitely aromatic. The partly reduced phthalic acids, of which a list is given in Table XXV, have been closely studied and are aliphatic in nature, adding on bromine readily and showing the characteristic behaviour of unsaturated compounds ; it is only when the third ethylenic link is introduced into the *cyclo*hexane ring that true aromatic character appears.

Many of the partially hydrogenated phthalic acids are obtained from dienes and maleic anhydride by the Diels-Alder reaction, which has been discussed previously (see p. 102).

AROMATIC DIBASIC ACIDS

These may best be divided into three main classes :—

(1) Those in which both carboxyls are directly attached to an aromatic residue.

---

[1] Kon and Nanji, *J.C.S.*, 1932, 2557.

[2] Staudinger and Ruzicka, *H. Chim. Acta*, 1924, 7, 206.

[3] Perkin, *J.C.S.*, 1894, **65**, 974.

[4] Evans, Ramage and Simonsen, *ibid.*, 1934, 1806 ; Ruzicka and Zimmermann, *H. Chim. Acta*, 1935, 18, 227 ; Rydon, *J.C.S.*, 1936, 593 ; 1937, 1340.

TABLE XXV

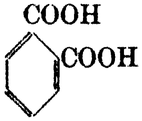
The Partially Reduced Phthalic Acids

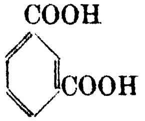
Position of the carboxyl groups		Position of the double bonds		Name	M.P.
A	B	C	D		
1	2	1	—	Δ¹-Tetrahydro-*o*-phthalic acid	120°
1	2	2	—	Δ²-Tetrahydro-*o*-phthalic acid	215°
1	2	3	—	Δ³-Tetrahydro-*o*-phthalic acid	?
1	2	4	—	Δ⁴-Tetrahydro-*o*-phthalic acid *cis*-	166°/174°
				trans- *rac.*	216°
				trans- *d* or *l*	166°
1	3	3	—	Δ³-Tetrahydro-*iso*phthalic acid	244°
1	3	4	—	Δ⁴-Tetrahydro-*iso*phthalic acid *cis*-	165°
				trans-	226°
1	4	1	—	Δ¹-Tetrahydro-*tere*phthalic acid	>300°*d*
1	4	2	—	Δ²-Tetrahydro-*tere*phthalic acid *cis*-	—
				trans-	228°
1	2	1	3	Δ¹, ³-Dihydrophthalic acid	?
1	2	1	4	Δ¹, ⁴-Dihydrophthalic acid	153°
1	2	2	4	Δ², ⁴-Dihydrophthalic acid	180°
1	2	2	5	Δ², ⁵-Dihydrophthalic acid	Anhydride 73-74°
1	2	2	6	Δ², ⁶-Dihydrophthalic acid	215°
1	2	3	5	Δ³, ⁵-Dihydrophthalic acid *cis*-	174°
				trans- *rac.*	210°
				trans- *d* or *l*	122°
1	3	1	5	Δ¹, ⁵-Dihydro-*iso*phthalic acid	255°
1	4	1	3	Δ¹, ³-Dihydro-*tere*phthalic acid	Decomp.
1	4	1	4	Δ¹, ⁴-Dihydro-*tere*phthalic acid	Sublimes
1	4	1	5	Δ¹, ⁵-Dihydro-*tere*phthalic acid	Decomp.
1	4	2	5	Δ², ⁵-Dihydro-*tere*phthalic acid *cis*-	>270°
				trans-	270°

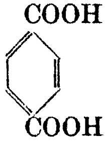
(2) Those in which one carboxyl only is attached to the aromatic residue.

(3) Those in which neither carboxyl is attached to the aromatic ring. Further subdivisions may be added to these, but they may best be indicated as the work proceeds.

The three parent substances of the first group are the phthalic acids :—


Phthalic acid


*Iso*phthalic acid


*Tere*phthalic acid

Phthalic acid was first prepared by Laurent[1] in 1836 by the oxidation of naphthalene with nitric acid ; Laurent suggested the names ' naphthalic ' or ' naphthesique ' acid for the new product, but Marignac[2] who deduced the correct empirical formula, $C_8H_6O_4$, pointed out that the acid did not belong to the naphthalene series and abbreviated the name to ' phthalic acid '. Schunck[3] in 1843 obtained the new acid during his investigations on the colouring matter of madder. In 1847, Cailletet obtained,[4] by the oxidation of rectified turpentine (terebene) with dilute nitric acid, an acid isomeric with phthalic acid, and called the new substance, *tere*phthalic acid ; it was later shown by Müller and de la Rue [1] to be identical with the acid obtained by oxidising Roman cumin oil. The third, or *iso*phthalic acid, was first obtained by the oxidation of *m*-xylene, then called ' *iso*-xylene '.[2]

---

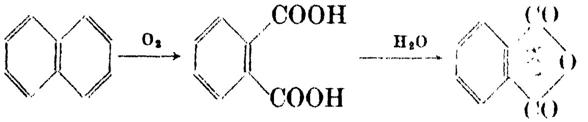
[1] Laurent, *Ann.*, 1836, **19**, 38.

[2] Marignac, *ibid.*, 1841, **38**, 13.

[3] Schunck, *ibid.*, 1843, **46**, 197.

[4] Cailletet, *Ann. Chim. Phys.*, 1847, 3, **21**, 28.

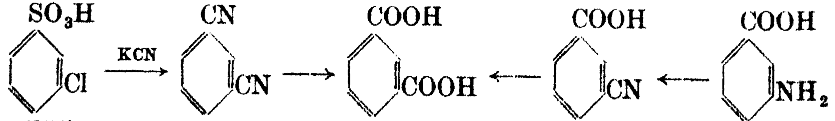
Phthalic acid is manufactured in considerable quantity by the oxidation of naphthalene. This was at one time effected by the laborious and wasteful use of nitric acid or chlorates until the discovery by Sapper, towards the end of the last century, that sulphuric acid could be used, in the presence of mercurous sulphate (at 275° C., the addition of 1 per cent. of mercurous sulphate quintuples the rate of oxidation of naphthalene).[3] Recently, vapour-phase oxidation has proved the most economic method of preparing phthalic acid ; naphthalene vapour and air are passed over a vanadium catalyst at about 450°. It should have been mentioned that from all the operations just mentioned, phthalic anhydride is isolated. Phthalic acid loses water quite readily and the extremely stable anhydride sublimes in long crystals, somewhat resembling asbestos in appearance.



Phthalic anhydride is frequently formed by the oxidation of *ortho*- di-substituted benzene derivatives, each side-chain being oxidised to carboxyl ; thus, *o*-xylene, *o*-diethylbenzene, *o*-toluic acid, *o*-methyl cinnamic acid all yield phthalic acid on oxidation. Phthalic acid crystallises in rhombic prisms ; it has no true m.p., being transformed into the anhydride on heating ; very rapid heating indicates a m.p. of approximately 200°. The loss of water from phthalic acid becomes appreciable at 140°. Phthalic acid is an extremely stable substance ; at 350° in the presence of lime it forms calcium benzoate, from which benzene can be obtained by raising the temperature. Halogens fail to act directly on phthalic acid, although in the presence of aqueous alkalies phthalic acid yields a 4-chloro derivative with chlorine. Under these conditions bromination does not occur ; to obtain the 4-bromo derivative, sodium phthalate must be treated with bromine and sodium hypobromite. Phthalic acid can be nitrated to a mixture of 3- and 4-nitro derivatives, in which the former predominates.

Little phthalic acid is used as such ; it is mainly converted to its anhydride and imide, the chemistry of which are discussed later.

Isophthalic acid is best obtained by the oxidation of *m*-xylene with calcium permanganate.[4] Probably the cheapest method of preparing it would be from *m*-chlorobenzene sulphonic acid (154), which, when heated with excess of potassium or sodium cyanide is converted to the dinitrile of *iso*phthalic acid (155) which, in turn, can be hydrolysed to *iso*phthalic acid (156) on boiling with concentrated hydrochloric acid.[5] Yet another alternative is the diazotisation of *m*-aminobenzoic acid, followed by a potassium cuprocyanide Sandmeyer decomposition, giving *m*-cyanobenzoic acid (157) which is readily hydrolysed to



(154) (155) (156) (157)

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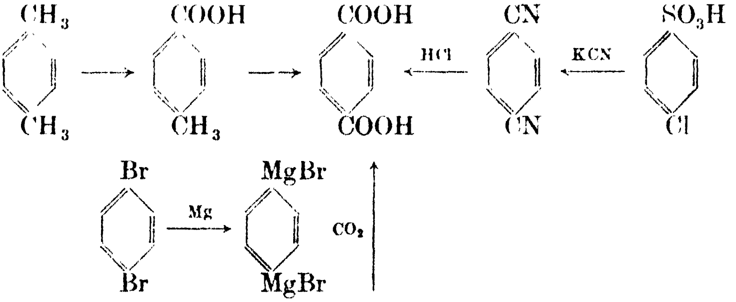
[1] Müller and de la Rue, *Ann.*, 1862, **121**, 86.
[2] Fittig, *ibid.*, 1868, **148**, 11.
[3] For an account of the discovery, see Levinstein, *J. Soc. Dyers*, 1901, **17**, 139.
[4] Ullmann and Uzbachian, *Ber.*, 1903, **36**, 1798.
[5] Bouther and Senhofer, *Ann.*, 1874, **174**, 236.

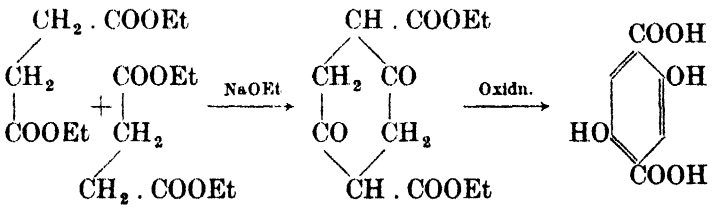
iso-phthalic acid. The acid forms needles, m.p. 348–349°, and is almost insoluble in cold water. The statement, often made, that *iso*phthalic acid forms no anhydride is incorrect,[1] although it forms no meta-bridge anhydride, it is readily converted by acetic anhydride to a non-volatile polymeric anhydride $\{C_6H_4(COO)_2O\}_n$. *Iso*phthalic acid may be distinguished from *tere*phthalic acid by the very soluble and brilliant crystals of its barium salt which crystallises with $6H_2O$; the corresponding barium *tere*phthalate is almost insoluble in water.

Terephthalic acid is best obtained by the alkaline permanganate oxidation of *p*-toluic acid; it can also be obtained from *p*-xylene by oxidation, whilst the formation of the acid from the Grignard compound of *p*-dibromobenzene and carbon dioxide is of constitutional significance:—



Terephthalic acid is frequently the end-point of the oxidation of many *para*-di-substituted aromatic and bicyclic compounds. It forms minute white needles which sublime without melting at about 300°, and which are almost insoluble in cold water (1 pt. in 67,000 at 10°).[2] Terephthalic acid forms a polymeric anhydride similar to that from *iso*phthalic acid; it also forms a diperterephthalic acid with great ease when terephthalyl chloride and concentrated hydrogen peroxide solutions are mixed; the diper-acid forms needles which detonate on heating.[3]

Attention is drawn to the relation of the succino-succinic derivatives to terephthalic acid. The product of the double internal Claisen condensation obtained when ethyl succinate reacts with sodium ethylate (158), gives on hydrolysis and oxidation a dihydroxyterephthalic acid (159).



(158) (159)

Many homologues of the phthalic acid family have been prepared mainly by methods entirely analogous to those already described; one novel method is, however, available for the manufacture of symmetrically alkyl substituted *iso*phthalic acids, namely, the condensation of three molecules of pyruvic acid with one of an aldehyde (160); the method is a general one, and has been used for the experimental production of uvitic acid (1-methylbenzene dicarboxylic acid-3, 5) (161) and its homologues.[1]

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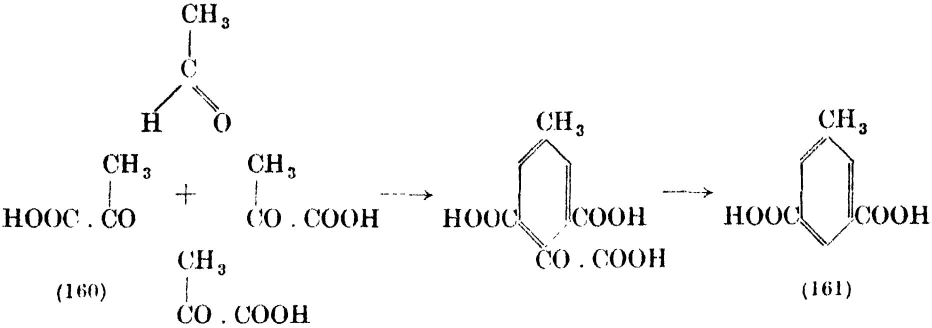
[1] Bucher and Slade, *J.A.C.S.*, 1909, **31**, 1319.

[2] Baeyer, *Ann.*, 1889, **251**, 284.

[3] Baeyer and Villiger, *Ber.*, 1901, **34**, 763.



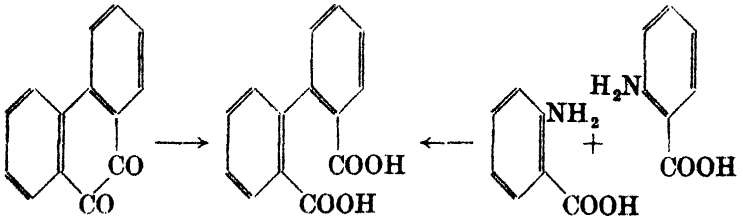
(160) (161)

The properties of the simple derivatives of the phthalic acid family and of their anhydrides is given in Table XXVI.

TABLE XXVI

Group positions				Acid M.P.	Anhydride M.P.
COOH	COOH	(a)	(b)		
1	2	3-Me	—	157°	110°
1	2	4-Me	—	152°	92°
1	2	3-Me	5-Me	181°	116°
1	2	3-Me	6-Me	143°	—
1	2	4-Me	5-Me	209°	208°
1	2	3, 4, 5, 6-Tetramethyl	—	249°	—
1	2	3-C(Me)$_3$	5-Me	173°	—
1	3	2-Me	—	229°	—
1	3	4-Me	—	332°	—
1	3	5-Me	—	298°	—
1	3	4-Et	—	267°	—
1	3	5-Et	—	264°	—
1	3	4-Me	6-Me	subl. 320°	—
1	3	4-CH(CH$_3$)$_2$	—	236°	—
1	3	5-CH(CH$_3$)$_2$	—	285°	—
1	3	2, 4, 6-Trimethyl	—	283°	—
1	3	5-CH$_2$CH(CH$_3$)$_2$	—	269°	—
1	4	2-Me	—	325°	—
1	4	2-Me	5-Me	subl. 340-350°	—
1	4	2-Me	6-Me	298°	—

To this group also belongs the diphenic acids ; ordinary diphenic acid (163) was discovered by Fittig and Ostermayer in 1873,[2] by the energetic oxidation of phenanthrenequinone (162) with chromic acid. It may equally well be obtained



(162) (163) (164)

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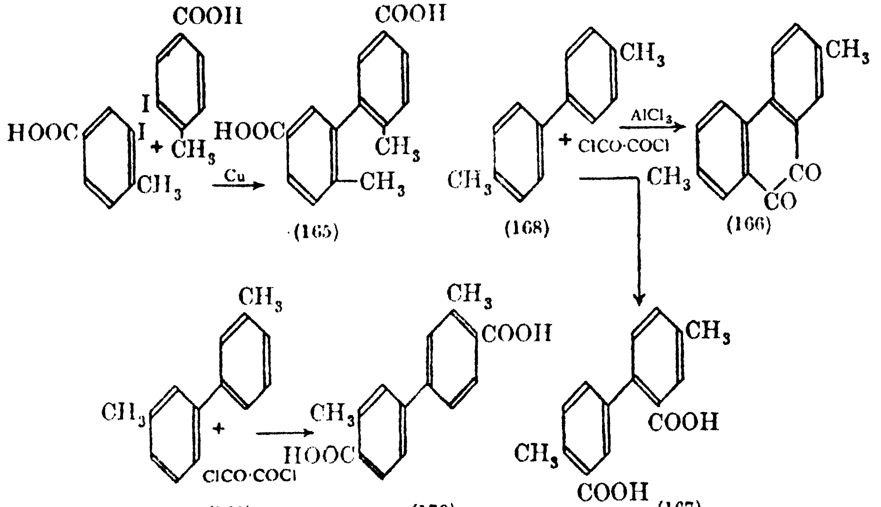
[1] Doebner, *Ber.*, 1890, **23**, 2379.

[2] Fittig and Ostermayer, *Ann.*, 1873, **166**, 367.

from diazotised anthranilic acid (164) in the presence of cuprous oxide, nitrogen being eliminated and a diphenyl derivative obtained.[1] The use of copper powder is particularly successful in the formation of diphenic acid derivatives. Thus *o*-iodo-*p*-toluic acid heated at 260° with copper powder gives a good yield of 2, 2′-dimethyl-5, 5′diphenic acid (165).[2]

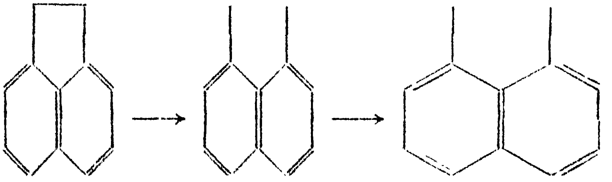


(165) (168) (166)

(169) (170) (167)

Liebermann[3] has recorded an interesting application of the Friedel-Crafts reaction in which oxalyl chloride is allowed to act on a substituted diphenyl in the presence of anhydrous aluminium chloride. In addition to some phenanthrenequinone derivative (166) there is also formed a substantial quantity of a diphenic acid. It is, however, impossible to tell the position which the entering carboxyl groups will occupy ; with 4, 4′-ditolyl (168) an unsymmetrical 2, 3′dicarboxylic acid (167) is formed ; with 3, 3′-ditolyl (169) the 4, 4′dicarboxylic acid (170) results. Further, the reaction of Döbner for production of uvitic acid and its homologues will, by the use of benzaldehyde, yields diphenyl 3, 5 dicarboxylic acid in moderate yield (see p. 557). The 2, 2-diphenic acids resemble phthalic acid in forming monomeric anhydrides by loss of water on heating. This behaviour is also characteristic of

Naphthalic acid (naphthalene 1, 8 dicarboxylic acid) (173), made by the vigorous oxidation of acenaphthene (171) ; it is formed as a by-product in the manufacture of acenaphthenequinone (172) for use in the manufacture of Ciba reds and scarlets. A singular reaction of 1, 8-naphthalic anhydride is its reaction



(171) (172) (173)

with mercuric acetate in aqueous solution, when one carbonyl group is replaced by mercury yielding a mercurianhydride (174). This compound reacts with bromine to give 8-bromo-α-naphthoic acid (175), a substance useful for synthetic work and capable of giving dinaphthyl dicarboxylic acid (176) on heating with copper powder.

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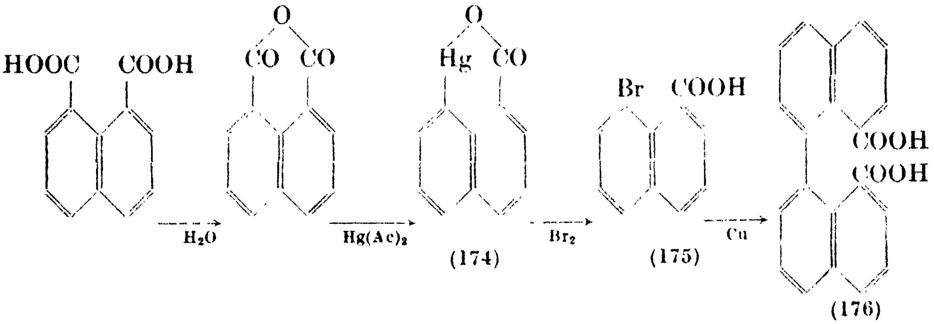
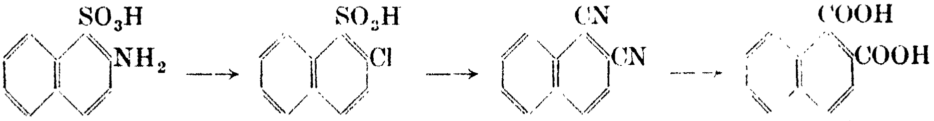
[1] Huntress, " Organic Syntheses ", Coll. Vol. I, page 216.
[2] Kenner and Witham, *J.C.S.*, 1913, **103**, 232.
[3] Liebermann, *Ber.*, 1911, **44**, 1453 ; 1912, **45**, 1186.



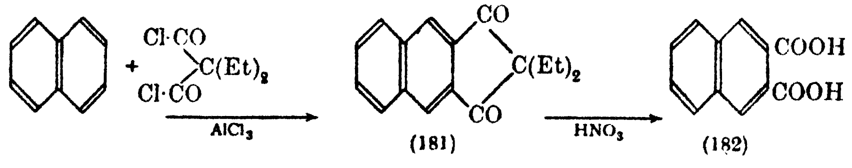
(174) (175) (176)

Most of the other nine theoretically possible naphthalene dicarboxylic acids are known. Both the 'adjacent' acids (1, 2 and 2, 3) form an anhydride quite readily. The 1, 2 acid is best obtained from Tobias acid (2-naphthylamine-1-sulphonic acid, made from the corresponding naphthol sulphonic acid *via* Bucherer's reaction) (177). The diazo-compound is allowed to react with cuprous chloride and forms the corresponding chloro-naphthalene sulphonic acid (178) which can be converted to dicyanonaphthalene (179) by fusion with potassium ferrocyanide and copper powder. Hydrolysis then gives naphthalene-1, 2-dicarboxylic acid (180).



(177) (178) (179) (180)

The 2, 3 acid is obtained by a variant of Liebermann's diphenic acid reaction; naphthalene and diethyl malonyl chloride enter into a Friedel-Crafts reaction in the presence of anhydrous aluminium chloride to give a naphthindanedione (181), which is oxidised by nitric acid to the 2, 3-dicarboxylic acid (182).

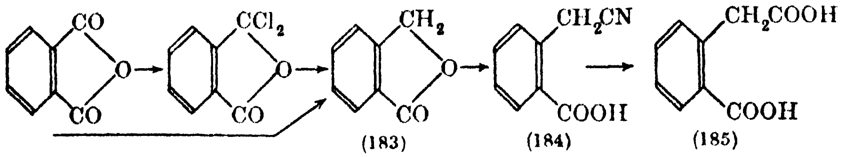


(181) (182)

AROMATIC DICARBOXYLIC ACIDS WITH ONLY ONE GROUP ATTACHED TO THE NUCLEUS

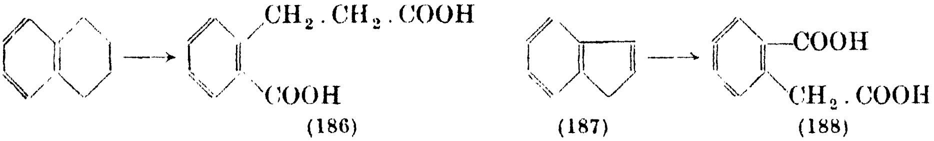
The most commonly encountered members of this series are the homophthalic acids, for which the following general methods of preparation are available.

(1) The anhydride or cyclic dichloride of any *ortho*-dicarboxylic acid of the aromatic series (e.g., phthalic anhydride or phthalyl chloride) can be reduced by zinc and acid to phthalide (183) or its homologues. Phthalides react with potassium cyanide to give the half nitriles of homophthalic acids (184) which can easily be hydrolysed to homophthalic acids themselves (185). (Cf. homocamphoric acid, p. 552.)

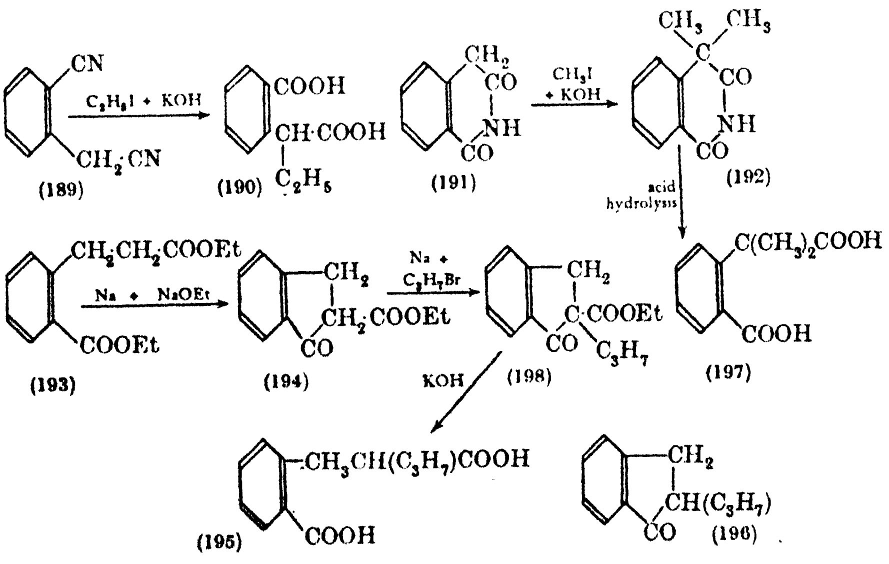


Other methods include

(2) The partial oxidation of alkyl benzoic acids, and of partially hydrogenated naphthalenes or indenes (analogous to the formation of adipic acid, q.v.). Thus, tetrahydronaphthalene[1] yields *o*-carboxyphenylpropionic acid (186); indene (187) gives *o*-carboxyphenylacetic (homophthalic) acid (188).[2]



Branched chain derivatives of this series can often be obtained by a series of abnormal alkylations. Thus, *o*-cyanophenylacetonitrile (189) alkylates on the —CH_2 using an alkyl iodide in presence of potash (190) whilst both hydrogens of the methylene group of homophthalimide (191) are alkylated by a similar process (192); the acid (197) may then be obtained by acid hydrolysis. Substituents on the α-carbon atom of *o*-carboxyphenylpropionic acid are introduced by allowing the ester of the acid (193) to react with sodium when an internal Claisen condensation takes place to give an indanone carboxylic ester (194); this ester is analogous to malonic ester and can be similarly alkylated (198); on hydrolysis the α-substituted open-chain ester (195) is obtained, together with some indanone derivative (196).



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[1] Bamberger and Kitschelt, *Ber.*, 1890, **23**, 1562.
[2] Hensler and Schieffer, *ibid.*, 1899, **32**, 29.

A few of the more important acids of this group are listed in Table XXVII.

TABLE XXVII

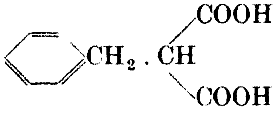
HOMOPHTHALIC ACID SERIES

$C_6H_4\begin{cases}COOH\ (a)\\(CH_2)_nCOOH\ (b)\end{cases}$ STRUCTURE					M.P. acid	M.P. anhydride
Position of (a)	Position of (b)	Value of n	Other substituents			
1	2	1	—	—	181°	141°
1	2	1	2_1-Me	—	147°	—
1	2	1	2_1, 2_1-diMe	—	123°	83°
1	2	1	2_1, 2_1-diMe	5-Me	131°	105°
1	2	1	2_1, 2_1-diEt	—	148°	53°
1	3	1	—	—	185°	—
1	4	1	—	—	238°	—
1	4	1	2-Me	—	199°	—
1	4	1	$3_1$5-diMe	—	285°	—
1	4	1	4_1-Me	—	223°	—
1	2	2	—	—	166°	—
1	3	2	—	—	177°	—
1	4	2	—	—	294°	—
1	2	2	2_2-Me	—	142°	—
1	3	2	3_2-Me	—	138°	—
1	2	3	—	— α	122°	Dimorphic
				β	138°	

There are, of course, in addition to the saturated acids, the cinnamic acid derivatives (*o*-, *m*- and *p*-carboxy cinnamic acid ; m.p. 202°, 275° and 355°) in which the side-chain is unsaturated.

DIBASIC ACIDS WITH NO CARBOXYL ATTACHED TO THE NUCLEUS

These are of two main classes : those dibasic acids in which the aryl group is purely a substituent, as in benzyl malonic acid (199) ; and those in which the



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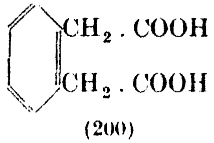
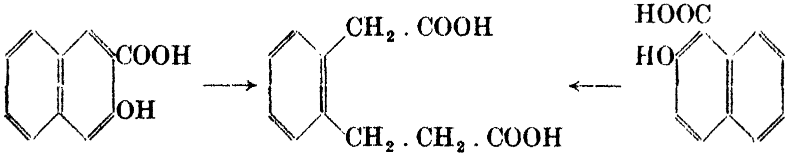


(200)

aryl nucleus forms a link between the two carboxyl groups as in *o*-phenylene diacetic acid (200). Among the general methods of preparing the members of the second group is the reduction of *o*-hydroxy naphthoic acids by sodium and amyl alcohol (cf. Einhorn's method of preparing pimelic acids).[1]



Perkin and Titley [2] used an indanone method for preparing the members of this series. The course of the reaction is sufficiently illustrated by the formulæ below :—

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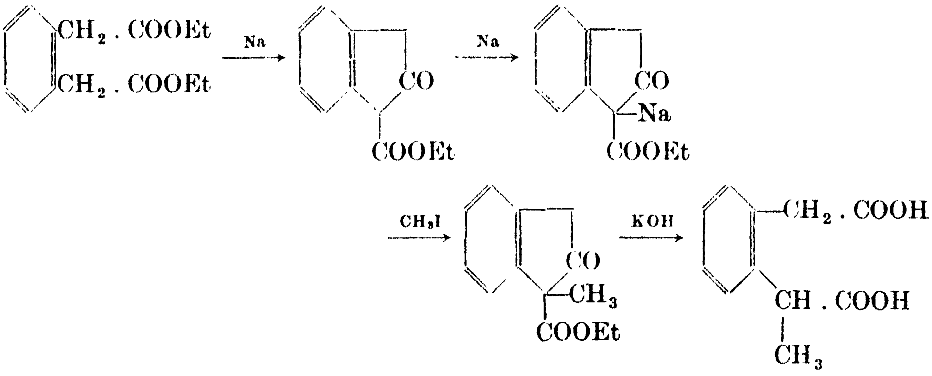
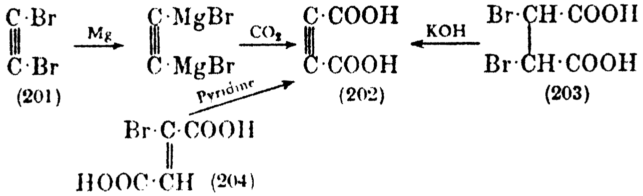
[1] Einhorn and Lumsden, *Ann.*, 1895, **286**, 257.
[2] Perkin and Titley, *J.C.S.*, 1922, **121**, 1562.



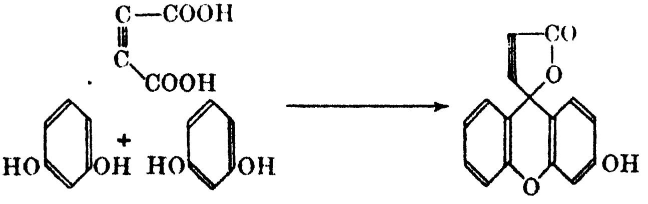
Dibasic Acetylenic Acids

Few members of this group are known ; the parent acid acetylene dicarboxylic acid, HOOC . C≡C . COOH (202), has a structure which admits of no substitution compounds, and is itself unstable, tending to pass into propiolic acid by loss of carbon dioxide. It may be obtained (*a*) by the action of alcoholic potash on dibromosuccinic acid (203) or by the action of pyridine on bromofumaric acid (204). It is probable that the best method is the action of carbon dioxide on an ethereal solution of the double Grignard compound of dibromoacetylene (201).



(201) (202) (203) (204)

Acetylene dicarboxylic acid forms large prisms, with two molecules of water of crystallisation. On heating it loses water of crystallisation and yields an anhydrous acid, m. 179°. It is a strong acid ($K_1 = 1{\cdot}85 \times 10^{-2}$) and gives a difficultly soluble acid potassium salt. No anhydride has been detected, but Misra and Dutt [1] point out that if heated with resorcin, acetylene dicarboxylic acid yields ' acetyleneins ' of the structure (205), analogous to fluorescein, and similarly coloured.



(205)

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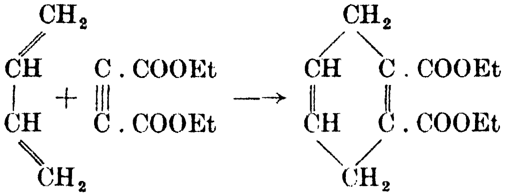
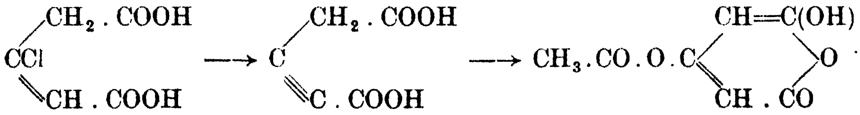
[1] Misra and Dutt, *J. Indian Chem. Soc.*, 1936, **13**, 98.

The use of acetylene dicarboxylic ester as one component of a Diels-Alder condensation with butadiene, gives rise to the ester of a dihydrophthalic acid of importance (206) in the consideration of the benzene theory (see Vol. III).



(206)

The next homologue of the series, glutinic acid (208), or pentyne-2-diacid 1, 5, is obtained from β-chloroglutaconic acid (207) by the action of alcoholic potash. It is a moderately stable crystalline substance, m. 159°. Like acetylene dicarboxylic acid it gives no anhydride; on digesting with acetic anhydride it yields the lactone (209). Baeyer[1] in his researches on this group, obtained these two acids :—



(207) (208) (209)

$HOOC.C{\equiv}C.C{\equiv}C.COOH$	Hexadiyne-2, 4, diacid-1, 6
$HOOC.C{\equiv}C.C{\equiv}C.C{\equiv}C.C{\equiv}C.COOH$	Decatetrayne-2, 4, 6, 8, diacid-1, 10

whilst Lespeau and Vavon[2] obtained the acid

$HOOC.C{\equiv}C.CH_2.CH_2.C{\equiv}C.COOH$	Octadiyne 2, 6-diacid-1, 8

All three acids are explosive, and the first two explode before reaching the m.p.; the octadiyne diacid (obtained from the dimagnesium derivative of dipropargyl and carbon dioxide) melts at 190°. The acids may be characterised by catalytic reduction to adipic, sebacic and suberic acids respectively.

POLYBASIC ACIDS

Aliphatic acids may be classified in the following way, which affords a convenient method of subdivision for the higher acids.

No. of carboxyl groups	Small figures indicate the number of carboxyl groups attached to an individual carbon atom						
I . .	a 1						
II . .	a 2	1 b 1					
III . .	a 3	2 b 1	1 1 c 1				
IV . .	a 4	3 b 1	2 c 2	2 1 d 1	1 1 1 e 1		
V . .	—	—	3 c 2	2 2 d 1	3 1 e 1	2 1 1 f 1	1 1 1 1 g 1

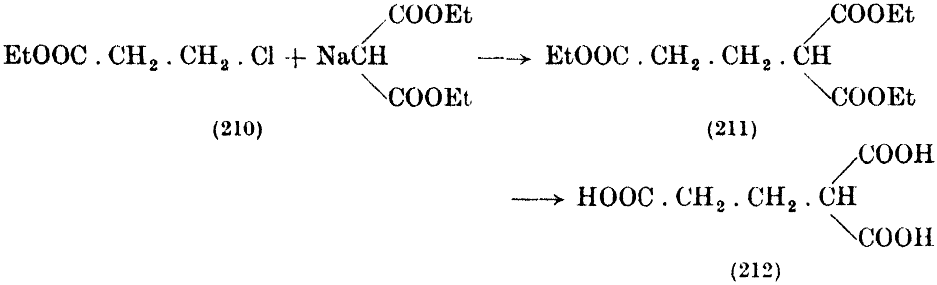
---

[1] Baeyer, *Ber.*, 1885, **18**, 677.

[2] Lespeau and Vavon, *C.R.*, 1909, **148**, 1332.

Group IIIa.—Acids carrying three carboxyl groups on one carbon atom are rare and usually can only be isolated as the esters. The trimethyl and triethyl esters of methane tricarboxylic acid, $HC(COOMe)_3$ and $HC(COOEt)_3$ are obtained by the action of heat on oxalomalonic esters.[1] They can also be prepared by the action of chloroformic ester on sodio-malonic ester.[2] These esters have the property of dissolving in alkalies and being reprecipitated unchanged on the addition of acids; the formation of these alkali derivatives enables them to take part in a variety of synthetic reactions, some of which are discussed in subsequent pages. The trimethyl ester, m. 45–46° and the tri-ethyl ester at 30°.

Group IIIb.—Members of this group are almost exclusively obtained by the malonic ester synthesis, as for example, the action of β-chloropropionic ester on the sodio derivative of malonic ester (210). The triethyl ester (211) is obtained

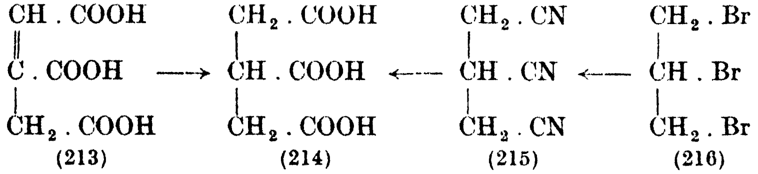


$$EtOOC.CH_2.CH_2.Cl + NaCH(COOEt)_2 \longrightarrow EtOOC.CH_2.CH_2.CH(COOEt)_2 \longrightarrow HOOC.CH_2.CH_2.CH(COOH)_2$$

(210) (211) (212)

and by cold alkaline hydrolysis yields the acid itself (212). Numerous examples of such acids have been prepared, a few of which are listed in Table XXVIII. More important, generally, and from a structural point of view, are the acids of *Group IIIc*, in which each carboxyl is attached to a different carbon atom.

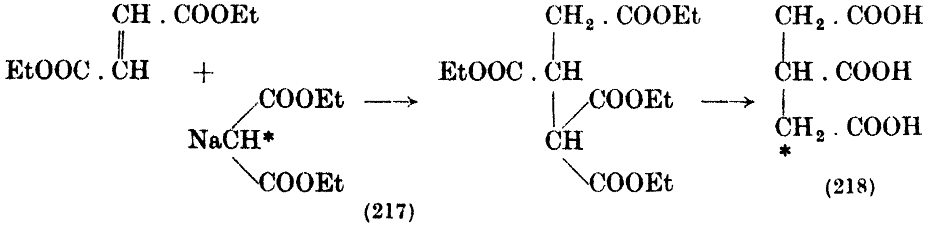
The parent acid of this group is usually called tricarballylic acid—but is sometimes more systematically referred to as 3-methylpentane-1, 5, 6-triacid. It was first prepared (214) in 1862 by Dessaignes by the reduction of aconitic acid (213) with sodium amalgam, and its structure was almost immediately confirmed by Simpson, who obtained it *via* the tricyano derivative (215) from 1, 2, 3-tribromopropane (216). In addition,



$$CH(COOH){=}C(COOH).CH_2.COOH \longrightarrow CH_2(COOH).CH(COOH).CH_2.COOH \longleftarrow CH_2(CN).CH(CN).CH_2.CN \longleftarrow CH_2Br.CHBr.CH_2Br$$

(213) (214) (215) (216)

tricarballylic acid can be prepared by the condensation of fumaric ester with the



$$EtOOC.CH{=}CH.COOEt + NaCH^*(COOEt)_2 \longrightarrow EtOOC.CH(CH_2.COOEt).CH(COOEt)_2 \longrightarrow CH_2(COOH).CH(COOH).CH_2^*.COOH$$

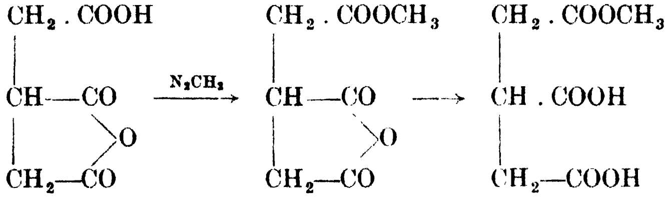
(217) (218)

sodio- derivative of malonic ester (217). The tetracarboxylic ester formed, readily hydrolyses to tricarballylic acid (218). The method is able to provide alkyl derivatives of tricarballylic acid, an alkyl group substituted into the methylene group of the initial malonic ester appears on the 2-carbon (*).

---

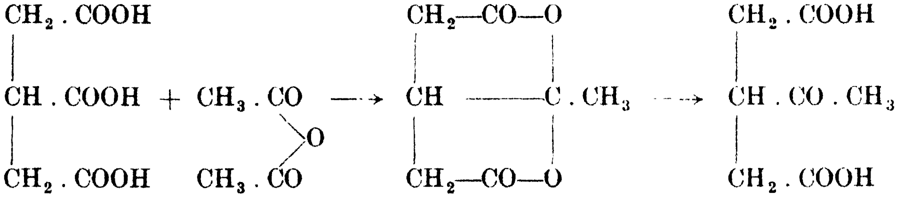
[1] Scholl and Egerer, *Ann.*, 1913, **397**, 357; Bouveault, *Bull. Soc. Chim.*, 1898, **19**, 79.
[2] Auwers and Auffenberg, *Ber.*, 1918, **51**, 1098.

Tricarballylic acid is found freely in nature, being present in vegetables such as sugar-beet, as the calcium salt. It is this calcium salt which forms such an intractable scale in the tubes of the vacuum evaporators used in the concentration of beet-sugar liquors. Tricarballylic acid forms large prisms, m. 165–166°, easily soluble in water. It forms a simple anhydride, m. 133°, when distilled under reduced pressure; the anhydride appears to have a structure[1] (219), in accordance with the action of diazomethane, when the



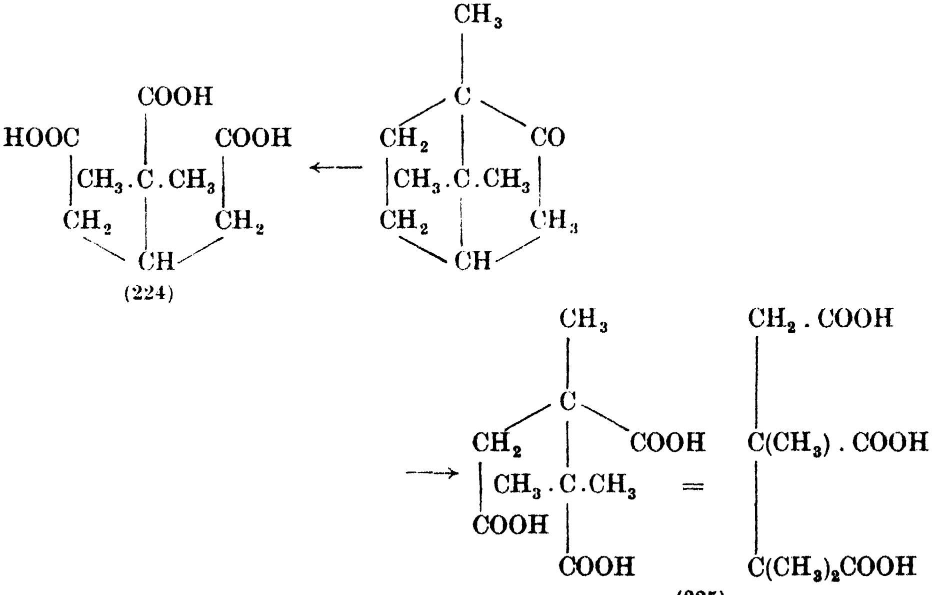
(219) (220) (221)

monomethyl ester of the anhydride (220) is obtained. This yields the monomethyl ester (221) on opening the anhydride ring. With acetic anhydride[2] (or analogous anhydride) tricarballylic acid reacts to form a dilactone (222) which on boiling with water gives the keto acid (223)



(222) (223)

Many of the homologues of tricarballylic acid are obtained during the oxidative degradation of the terpenes; camphoronic acid (225) is an excellent example of



(224)

(225)

Trimethyltricarballylic acid

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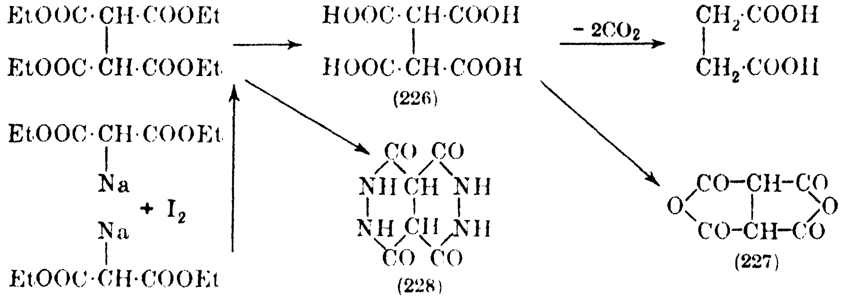
[1] Malachowski, *Zentr.*, 1929, **11**, 2175.

[2] Fittig, *Ber.*, 1897, **30**, 2145.

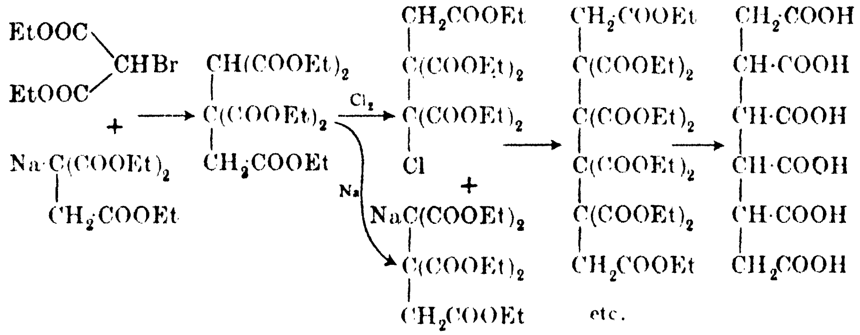
such an acid ; it is derived by oxidation of camphor and its synthesis has been effected (see Chap. IX). The presence of an asymmetric carbon atom in camphoronic acid leads to optical activity ; the inactive form has m. 172°, the *d*- and *l*- forms melting at 156–158°.

Some *iso*-camphoronic acid (224) is produced at the same time as the main product, camphoronic acid, when camphor is oxidised by nitric acid. Many other examples of this family are known—some are listed in Table XXVIII.

Of the aliphatic saturated tetrabasic acids, methane tetracarboxylic acid, $C(COOH)_4$ is only known as its esters, the free acid immediately decomposing. Of the remainder, many are obtained by the action of iodine or dihalides on the sodio-derivative of malonic ester. In this way ethane tetracarboxylic acid (often called acetylene tetracarboxylic acid) (226) is obtained, in needles, m. 168°. It readily loses carbon dioxide on heating, yielding succinic acid, and is capable of yielding an interesting double anhydride (227) when digested with acetic anhydride,[1] whilst by the action of hydrazine on the ester, a cyclic hydrazide (228) can be produced.



Many acids containing more than four carboxyl groups are known, indeed, Bischoff[2] by a sequence of reactions shown in the formulæ below obtained aliphatic acids with up to fourteen carboxyl groups. Little is known about the higher polybasic acids and their consideration need not be further pursued.



UNSATURATED AND ALICYCLIC POLYBASIC ACIDS

Aconitic acid (232) is the best known of the unsaturated tribasic aliphatic group, being widely distributed naturally and having a long history. Originally isolated by Peschier[3] in 1820, from *Aconitum* species, it has subsequently been

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[1] Philippi and Hanusch, *Ber.*, 1920, **53**, 1300.

[2] Bischoff, *ibid.*, 1888, **21**, 2114.

[3] Cited by Trommsdorff, *Neu. Journ. Pharm.*, 1820, **5**, 1, 93.

TABLE XXVIII

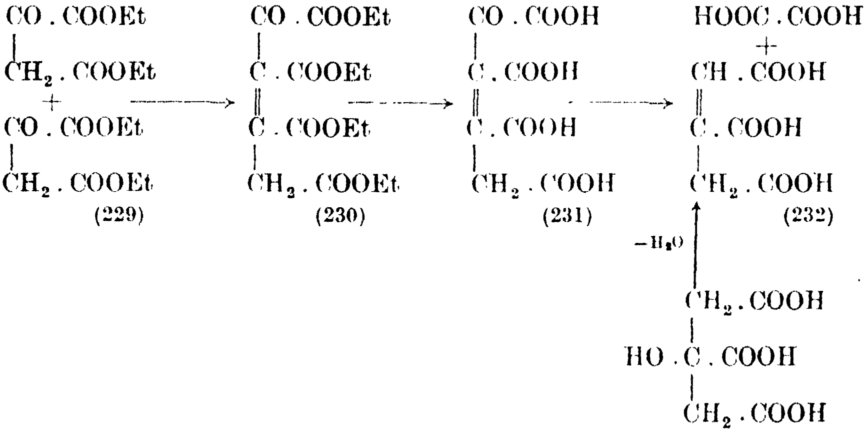
SOME SATURATED POLYBASIC ALIPHATIC ACIDS

Name	Structure	M.P. acid		B.P. triethyl ester
2-Carboxysuccinic acid	$HOOC . CH_2 . CH(COOH)_2$		159°	156–158°/15 mm.
2-Methyl-2-carboxysuccinic acid	$HOOC . CH_2 . C(CH_3)(COOH)_2$		170°	274°
3-Methyl-2-carboxysuccinic acid	$HOOC . CH(CH_3) . CH(COOH)_2$	*rac.* *l*-	146° 150°	178–180°/25 mm. —
2, 3-Dimethyl-2-carboxysuccinic acid	$HOOC . CH(CH_3) . C(CH_3)(COOH)_2$		157°	190°/55 mm.
3, 3-Dimethyl-2-carboxysuccinic acid	$HOOC . C(CH_3)_2 . CH(COOH)_2$		167°	—
2-Carboxyglutaric acid	$HOOC . CH_2 . CH_2 . CH(COOH)_2$		125°	158°/12 mm.
2-Methyl-2-carboxyglutaric acid	$HOOC . CH_2 . CH_2 . C(CH_3)(COOH)_2$		134°	166°/20 mm.
3-Methyl-2-carboxyglutaric acid	$HOOC . CH_2 . CH(CH_3)CH(COOH)_2$		139°	165°/11 mm.
4-Methyl-2-carboxyglutaric acid	$HOOC . CH(CH_3)CH_2 . CH(COOH)_2$		161°	160°/14 mm.
2, 3-Dimethyl-2-carboxyglutaric acid	$HOOC . CH_2 . CH(CH_3)C(CH_3)(COOH)_2$		166°	161°/10 mm.
2, 4-Dimethyl-2-carboxyglutaric acid	$HOOC . CH(CH_3)CH_2 . C(CH_3)(COOH)_2$	*rac*- *d*- or *l*-	155° 146°	158°/10 mm. —
3, 3-Dimethyl-2-carboxyglutaric acid	$HOOC . CH_2 . C(CH_3)_2 . CH(COOH)_2$		173°	174°/43 mm.
3, 4-Dimethyl-2-carboxyglutaric acid	$HOOC . CH(CH_3)CH(CH_3)CH(COOH)_2$		144°	—
4, 4-Dimethyl-2-carboxyglutaric acid	$HOOC . C(CH_3)_2 . CH_2 . CH(COOH)_2$		—	147°/10 mm.
2, 3, 3-Trimethyl-2-carboxyglutaric acid	$HOOC . CH_2C(CH_3)_2C(CH_3)(COOH)_2$		190°	—
2, 4, 4-Trimethyl-2-carboxyglutaric acid	$HOOC . C(CH_3)_2CH_2C(CH_3)(COOH)_2$		145°	181°/25 mm.

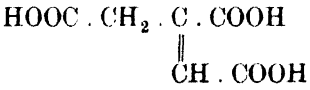
2-Carboxyadipic acid	$HOOC . CH_2 . CH_2 . CH_2 . CH(COOH)_2$		140°	176°/18 mm.
2-Carboxypimelic acid	$HOOC . CH_2 . CH_2 . CH_2 . CH_2 . CH(COOH)_2$			172–176°/19 mm.
2-Methyltricarballylic acid	$HOOC . CH_2 . CH(COOH) . CH(CH_3)COOH$	*cis-* *trans-*	186° 140°	— —
3-Methyltricarballylic acid	$HOOC . CH_2 . C(CH_3)(COOH)CH_2 . COOH$		166°	—
2, 2-Dimethyltricarballylic acid	$HOOC . CH_2 . CH(COOH)C(CH_3)_2COOH$		158°	172–174°/19 mm.
2, 3-Dimethyltricarballylic acid	$HOOC . CH_2 . C(CH_3)(COOH)CH(CH_3)COOH$		167°	—
2, 4-Dimethyltricarballylic acid	$HOOC . CH(CH_3)CH(COOH)CH(CH_3)COOH$	*trans-* *cis I-* *cis- II-*	207° 176° 149°	— — —
2, 2, 3-Trimethyltricarballylic acid	$HOOC . CH_2 . C(CH_3)COOH . C(CH_3)_2COOH$	*rac.* *d-* or *l-*	172° 158°	137° 130°
2, 2, 4, 4-Tetramethyltricarballylic acid	$HOOC . C(CH_3)_2 . CH(COOH)C(CH_3)_2COOH$		140°	—
Methane triacetic acid	$CH(CH_2 . COOH)_3$		126°	202°/19 mm.
Ethane triacetic acid	$CH_3 . C(CH_2 . COOH)_3$		172°	185–187°/22 mm.
				B. p. polyethyl ester
Ethane tetracarboxylic acid	$(HOOC)_2 . CH . CH(COOH)_2$		168°	305°
Methylene dimalonic acid	$(HOOC)_2CH . CH_2 . CH(COOH)_2$		169°	185–190°/6 mm.
Ethylene dimalonic acid	$(HOOC)_2CH . CH_2 . CH_2 . CH(COOH)_2$		—	220°/10 mm.
2-Carboxytricarballylic acid	$HOOC . CH_2 . CH(COOH)CH(COOH)_2$		153°	201°/14 mm.
Carboxy methane triacetic acid	$HOOC . C(CH_2 . COOH)_3$		209°	—
2, 3-Dicarboxytricarballylic acid	$HOOC . CH_2 . C(COOH)_2 . CH(COOH)_2$		150°	m. 87–88°
Ethane hexacarboxylic acid	$(HOOC)_3C . C(COOH)_3$		—	m. 101–102°

extracted from a large variety of plants, especially the *Equisetaceæ*, *Delphinium consolida*, *Adonis vernalis* and *Achillea millefolia*, together with sugar-cane and sugar-beet.

Aconitic acid is usually prepared from citric acid by fusion (232), when it loses water to give aconitic acid. It can also be prepared by the auto-condensation of two molecules of oxalacetic ester (229) whereby an

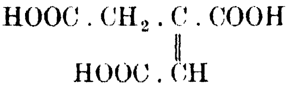


unsaturated tetracarboxylic ester is formed (230); this on hydrolysis yields aconitic acid and oxalic acid. The acid exists in two forms; that normally prepared is of the constitution (234), usually referred to as '*trans*'. Malachowski[1] showed that the normal or *trans*-form, m. 194–195°, is converted by acetic



$$\begin{array}{l}\mathrm{HOOC\,.\,CH_2\,.\,C\,.\,COOH}\\ \qquad\qquad\quad \| \\ \qquad\qquad\mathrm{CH\,.\,COOH}\end{array}$$

cis-
(233)

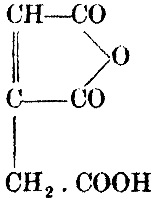


$$\begin{array}{l}\mathrm{HOOC\,.\,CH_2\,.\,C\,.\,COOH}\\ \qquad\qquad\quad \| \\ \qquad\mathrm{HOOC\,.\,CH}\end{array}$$

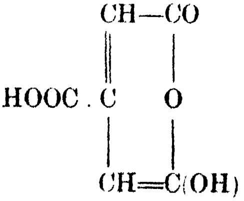
trans-
(234)

anhydride to a mixture of *trans*-anhydride (m. 134-135°) and *cis*-anhydride (m. 78°) which can be separated by taking account of their differing solubilities in chloroform. The *cis*-anhydride on treatment with ice-cold water yields *cis*-aconitic acid (233) as a crystalline mass, m. 125°.

Surprisingly, aconitic acid forms two anhydrides, but although these are referred to as *cis*- and *trans*-, they represent two different types of ring (235) and (236); they are both easily hydrated to their respective acids. Aconitic



(235)



(236)

acid gives a pink colour[2] with acetic anhydride (Taylor's reaction); this can be intensified by adding a few drops of ether and water to the acetic anhydride containing the aconitic acid. A blue ether layer over a pink aqueous substratum is formed. This test will detect 0·01 mgm. of aconitic acid.

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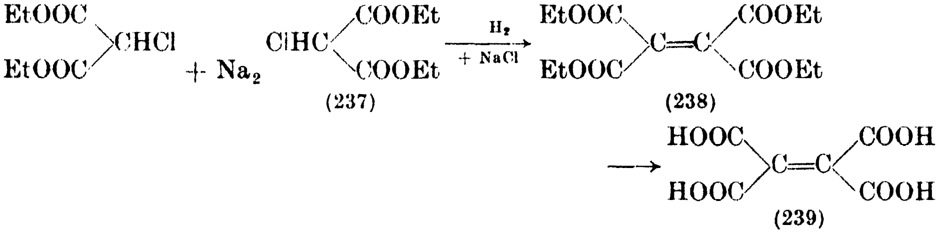
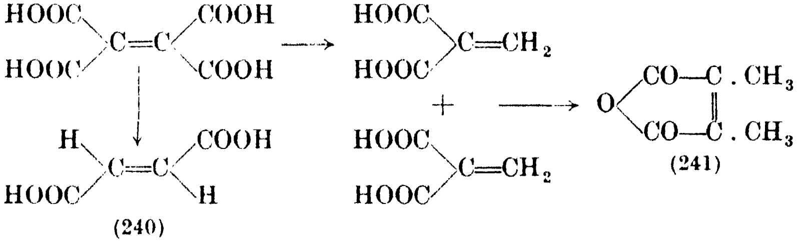
[1] Malachowski *et al.*, *Ber.*, 1928, **61**, 2521, 2525.
[2] Taylor, *J.C.S.*, 1919, **115**, 887.

Of the unsaturated tetracarboxylic acids, ethylene tetracarboxylic acid (239) is most frequently encountered. It may be obtained by the action of sodium on chloromalonic ester (237). Ethylene tetracarboxylic acid forms large prisms



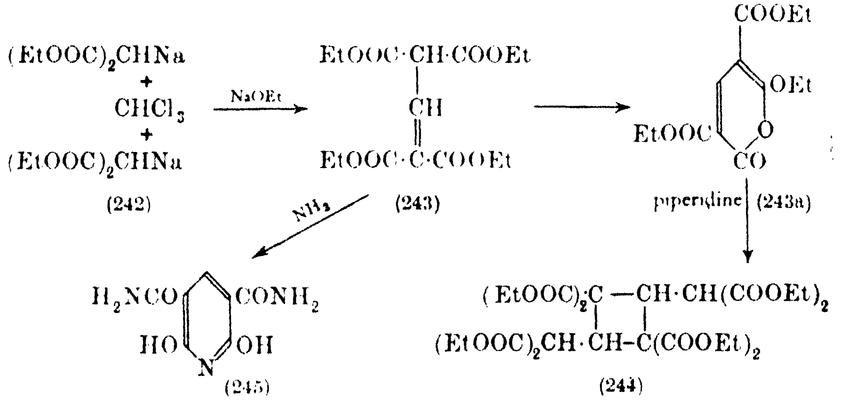
(237) (238) (239)

(1½H_2O), and decomposes on rapid heating to give dimethyl maleic anhydride (241); at the same time some fumaric acid (240) is formed.



(240) (241)

Among other members of this group, 1, 3-dicarboxyglutaconic acid may be mentioned, for its protean tendencies in ring formation. The tetra-ethyl ester (243) prepared by the action of chloroform on sodio-diethyl malonate



(242) (243) (245) (244)

(242) yields a coumalic ester derivative (243) on distillation at 20 mm.[1] With piperidine the ester gives an octa-ester of a *cyclo*butane structure (244). With ammonia, some malonamide is formed, together with the diamide of 2, 6-dihydroxypyridine-3, 5 dicarboxylic acid (245).

Of the yet higher polybasic unsaturated acids, few have been isolated as such, although many esters containing from five to eight carbethoxy groups are known. These are mainly intermediates in the malonic ester syntheses, and some are illustrated in Appendix II to this chapter.

The poly acids of the *cyclo*-alkane group occupy an important position in the elucidation of stereochemical problems, and in several instances the isolation of the theoretical number of isomeric acids has played an important part in confirming stereochemical conceptions.

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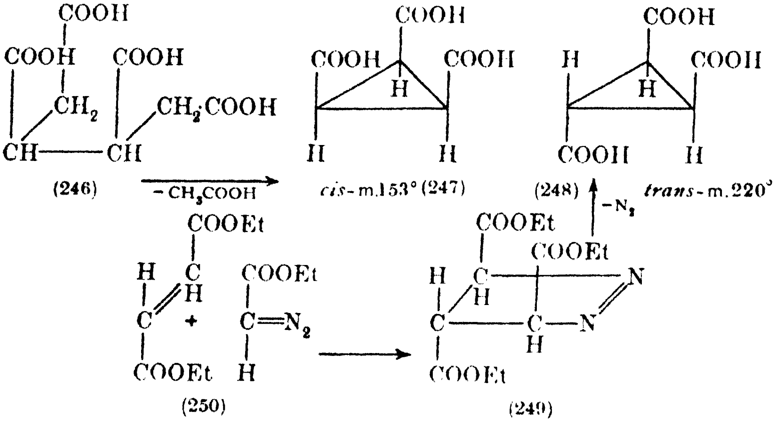
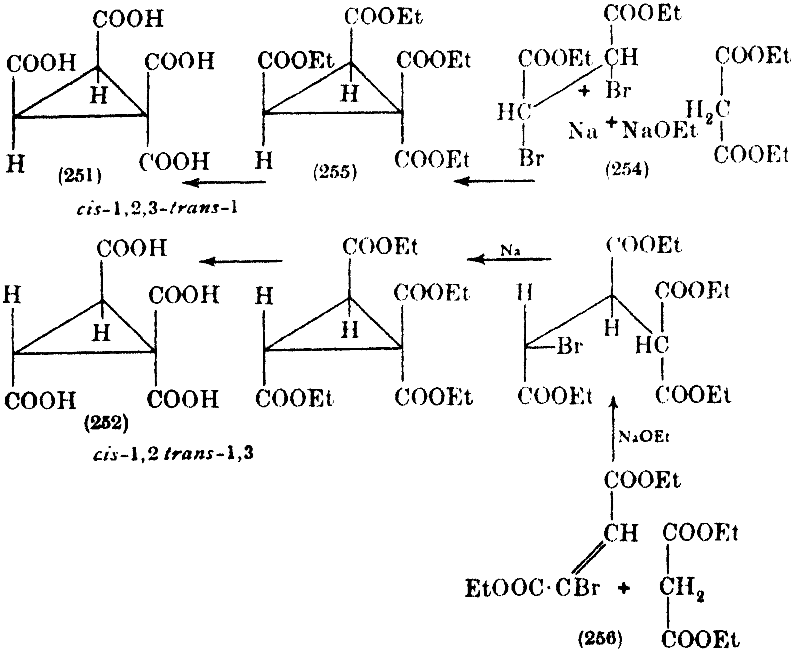
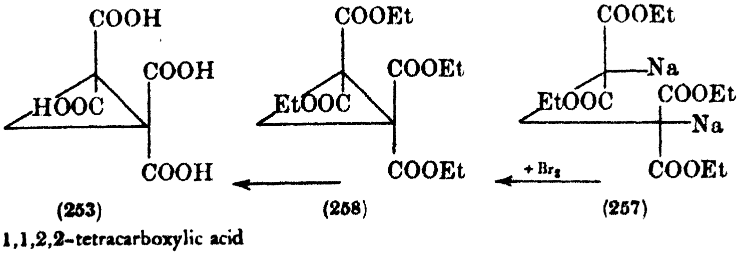
[1] Gutzeit, Weiss and Schaeffer, *J. Pr. Chem.*, 1909, **80**, 416, 439.

Thus, *cyclo*propane tricarboxylic acid can exist in two forms, *cis-* and *trans-* (247) and (248). Both these structures have been prepared, the *cis-* form by heating butane 1, 2, 3, 4-tetracarboxylic acid (246), which yields *cis-cyclo*propane-1, 2, 3-tricarboxylic acid (247) and acetic acid. The *trans-* acid, is



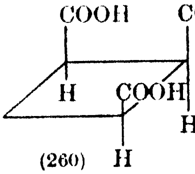




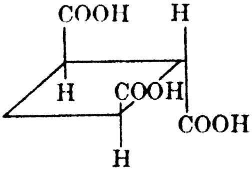
obtained by decomposing the pyrazolin tricarboxylic acid (249) obtained, in turn, from its ester (from diazoacetic ester and fumaric ester) (250).

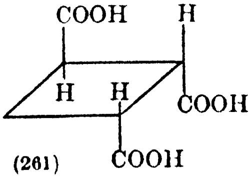
There are three possible tetracarboxylic acids of *cyclo*propane having the configurations set out in (251) to (253). They are all known. The *cis*-1, 2, 3, *trans*-1 compound is made by the action of dibromosuccinic ester on sodio-malonic ester in the presence of sodium ethoxide (254); the ester so formed (255) can be hydrolysed to the acid, which forms small white needles melting with decomposition at 200°. The *cis*-1, 2 *trans*-1, 3 acid, is made by an analogous process from bromo-maleic ester, malonic ester and sodium ethoxide (256). The 1, 1, 2, 2-tetracarboxylic acid (253) is prepared *via* the ester, from the ester of propane tetracarboxylic acid (258), itself readily obtained from methylene chloride and sodio-malonic ester (257). The disodium derivative of the propane dicarboxylic ester is treated with bromine.

*Cyclo*butane polycarboxylic acids are not so readily prepared, the tricarboxylic acid (259) can be obtained by a malonic ester synthesis. It exists



(260)





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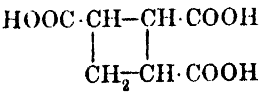
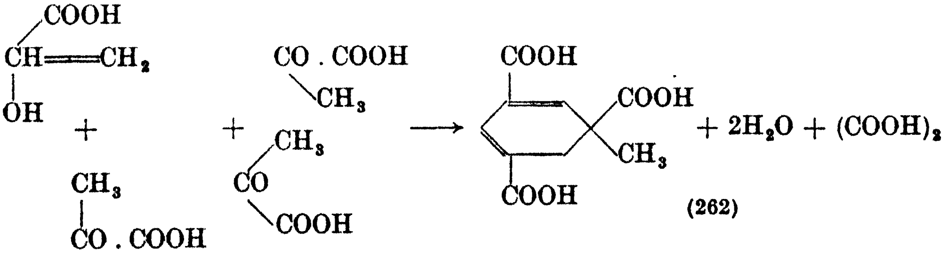


(259)

in two forms, a *cis*-form, m. 171°, which appears to have the structure (260), and a *trans*-form having the structure (261). Several tetracarboxylic acids of *cyclo*butane have been obtained but they offer few points of importance. Some of the more commonly met with *cyclo*butane and *cyclo*pentane derivatives of the series are shown in Table XXIX on page 574.

The field of *cyclo*pentane and *cyclo*hexane polybasic acids has been fairly widely explored; the malonic ester method has been found capable of yielding almost all the theoretically possible structures, although in some cases the configurations are obscure. An interesting casual method of formation of 1-methyl-1, 2-dihydrotrimesic acid (262), is the condensation of four molecules of pyruvic acid (263), one of which reacts in the enolic form.[1]



(262)

(263)

It will have been noted that nothing is implied in Table XXIX about the stereo-chemical identity of the particular acid isolated; little is known about the complicated stereo-chemical relations of the higher *cyclo*alkane polybasic acids; for instance, there are over eighty theoretically possible *cyclo*hexane hexacarboxylic acids, several of which should be capable of optical resolution; few of these are known, and the field has remained unexplored.

[1] Wolff and Heipp, *Ann.*, 1899, **305**, 135.

TABLE XXIX

Polybasic Acids of the *cyclo*Butane, *cyclo*Pentane and *cyclo*Heptane Series

Name	M.P. or B.P.		
	Acid M.P.	Ethyl ester B.P.	Anhydride
*cyclo*Propane hexacarboxylic acid (1, 1, 2, 2, 3, 3)	—	197-202°/12 mm.	
*cyclo*Butane-1, 1, 2, 2-tetracarboxylic acid	200° decomp.		
*cyclo*Butane-1, 1, 3, 3-tetracarboxylic acid	—	220-250°/15 mm.	
*cyclo*Butane-1, 1, 2, 4-tetracarboxylic acid	—	195-198°/12 mm.	
*cyclo*Butane-1, 2, 3, 4-tetracarboxylic acid	285-287°	(Methyl) m. 103°	
*cyclo*Butane-1, 1, 2, 2, 3, 4-hexacarboxylic acid	—	m. 80°	
*cyclo*Pentane-1, 1, 2, 2-tetracarboxylic acid	200-220° decomp.	192-195°/12 mm.	
*cyclo*Pentane-1, 1, 2, 4-tetracarboxylic acid	190° decomp.	—	
*cyclo*Pentane-1, 1, 3, 3-tetracarboxylic acid	186-188°	225-227°/15 mm.	
*cyclo*Pentane-1, 1, 2, 5-tetracarboxylic acid	—	214-216°/23 mm.	
*cyclo*Pentane-1, 1, 2, 4, 4-pentacarboxylic acid	—	234-236°/15 mm.	
*cyclo*Pentane-1, 1, 2, 2, 4, 4-hexacarboxylic acid	210-212°	—	
*cyclo*Hexane-1, 1, 3, 3-tetracarboxylic acid	Decomp.	243-245°/50 mm.	
*cyclo*Hexane-1, 2, 3, 4-tetracarboxylic acid	168°	238°/15 mm.	Dianhydride m. 223-225°
*cyclo*Hexane-1, 2, 4, 5-tetracarboxylic acid	217°	(Methyl m. 88°)	
*cyclo*Hexane-1, 1, 4, 4-tetracarboxylic acid	249-250°	m. 76-77°	
*cyclo*Hexane-1, 2, 3, 4, 5, 6-hexacarboxylic acid		α-(Methyl) m.125° β-(Methyl) m.125°	
*cyclo*Hexane-1, 1, 2, 4, 4, 5-hexacarboxylic acid		α-(Methyl) m.181° α-(Methyl) 220°/223° mm.	
*cyclo*Heptane-1, 1, 3, 3, 5, 6-hexacarboxylic acid	177°	(Methyl) m. 128°	

The Aromatic Polybasic Acids

All eight of the polybasic benzene carboxylic acids are known, and their properties are summarised in Table XXX. Mellitic acid was among the earliest substances of the aromatic series to become the subject of experiment. Klaproth in 1799 examined honeystone, which is a honey-coloured prismatic mineral frequently found amongst the coal measures. Klaproth showed honeystone to be the aluminium salt of a new acid, but the state of chemical knowledge at the time was such that he was unable to speculate on the structure of the new acid which he termed ‘ mellitic ’ acid. Several investigators were attracted to the substance, but it is probable that Wöhler [1] was the first to obtain the pure acid, and with Liebig [2] he established the empirical formula of the acid as $(C_2HO_2)_n$, but inclined towards $n = 2$ as the true molecular formula. They attempted to prepare synthetic mellitic acid by the chlorination of succinic acid:—

$$C_4H_6O_4 + 2Cl_2 \longrightarrow C_4H_2O_4 + 4HCl$$

Erdmann [3] obtained a new acid, pyromellitic acid, by heating mellitic acid and at the same time isolated a trace of aromatic oil which led him to the opinion

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[1] Wöhler, *Pogg. Ann.*, 1826, **7**, 325.
[2] Liebig and Wöhler, *ibid.*, 1830, **18**, 161.
[3] Erdmann, *J. Pr. Chem.*, 1851, **52**, 432.

TABLE XXX

BENZENE POLYBASIC ACIDS

Systematic name	Common name	M.P.		
		Acid	Mono anhydride	Poly methyl ester
Benzene-1, 2, 3-tricarboxylic acid	Hemimellic acid	200°	193-196°	101-102°
Benzene-1, 2, 4-tricarboxylic acid	Trimellitic acid	215-217°	163-165°	-13°, b. 194°/12 mm.
Benzene-1, 3, 5-tricarboxylic acid	Trimesic acid	360°		143°
Benzene-1, 2, 3, 4-tetracarboxylic acid	Mellophanic acid	238-240°	(di) 193-196°	132-135°
Benzene-1, 2, 3, 5-tetracarboxylic acid	Prehnitic acid	252-262°	(mono) 239°	107-109°
Benzene-1, 2, 4, 5-tetracarboxylic acid	Pyromellitic acid	275-270°	(di) 286°	138-142°
Benzene pentacarboxylic acid	-	233°	—	146-148°
Benzene hexacarboxylic acid	Mellitic acid	288° (closed capillary)	sublimes	188°

that the acid might be a member of the aromatic series ; a suspicion confirmed by the investigations of Baeyer,[1] who distilled the acid with soda-lime and obtained benzene itself. His remarks on the subject are worth quoting *in extenso* :

> " According to the formula $C_4H_2O_4$, which was then universally accepted, I had to expect the evolution of acetylene, just as ethyl hydride is obtained by igniting succinic acid with lime :
>
> $$C_4H_6O_4 = C_2H_6 + 2CO_2$$
> $$C_4H_2O_4 = C_2H_2 + 2CO_2$$
>
> When I obtained benzene, I at first thought that a condensation of the acetylene had taken place at the high temperature employed, this having been recently observed by Berthelot, when this gas is kept at a red-heat for some time. If this had been the case, mellitic acid ought to have yielded an isomeride of fumaric or succinic acid on reduction :
>
> $$C_4H_2O_4 + H_2 = C_4H_4O_4$$
> $$C_4H_6O_4 + H_4 = C_4H_6O_4$$
>
> On treatment with sodium amalgam, however, mellitic acid was converted into an acid, which did not volatilize on heating, but carbonized like sugar and at the same time produced a smell of burnt sugar. Mellitic acid must, therefore, have a much more complicated composition than had hitherto been believed, and it appeared probable that the products of its decomposition with soda-lime are not formed by condensation but are rather portions of a single molecule. According to this view, the simplest formula for mellitic acid is $C_{12}H_6O_{12}$ and it is a benzene in which all the hydrogen atoms have been replaced by carboxyl groups, COOH."

Later, Schulze[2] obtained mellitic acid by the oxidation of charcoal with alkaline permanganate and Bartoli and Papasogli[3] by the electrolysis of potassium hydroxide solutions with graphite blocks. It would appear, therefore, that coal, charcoal and graphite contain assemblages of carbon atoms, in which a hexagonal ring forms an integral part and is capable of furnishing benzene hexacarboxylic acid on oxidative degradation.

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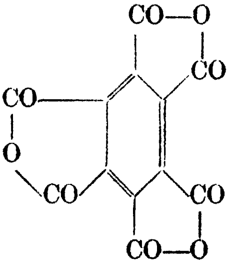
[1] Baeyer, *Annalen Supplement* 1870, No. 7, p. 1.
[2] Schulze, *Ber.*, 1871, **4**, 802, 806.
[3] Bartoli and Papasogli, *Gazz. Chim. Ital.*, 1883, **13**, 37.

During recent years various improved methods for preparing mellitic acid have been introduced, notably that of Meyer and Raudnitz,[1] in which carbon black is oxidised by nitric acid in the presence of vanadium pentoxide to 85–90 per cent. of its weight of crude mellitic acid, giving 35 to 40 per cent. of its weight of pure mellitic acid. Feist has also obtained up to 60 per cent. yields of mellitic acid by heating tetrachlorophthalic acid with potassium cyanide and hydroxide, copper cyanide and water under pressure.[2]

Apart from its unusual mode of occurrence, mellitic acid offers little of significance in its properties ; it is easily recrystallised from alcohol in needles, and is very soluble in water. Its aluminium salt, $Al_2C_{12}O_{12}$, crystallises with $18H_2O$. Mellitic acid behaves normally as a hexacarboxylic acid, giving a hexamethyl and hexaethyl ester (m. 188° and 73° respectively). It gives a hexachloride, and a trianhydride having the structure (264) which is free from hydrogen ($C_{12}O_9$). It is a crystalline substance, resembling phthalic anhydride itself. With phenol and stannic chloride it forms a mellitein (analogous to a phthalein) which has the properties of an indicator, being deep violet in alkaline solution and colourless in acid solution ; the structure of this mellitein is probably as depicted in (265).



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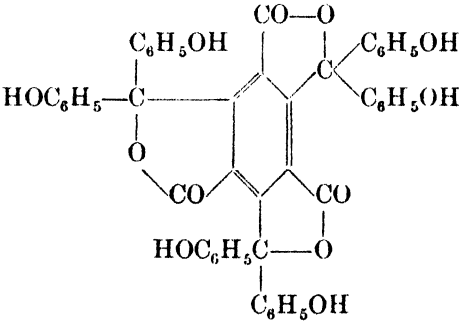
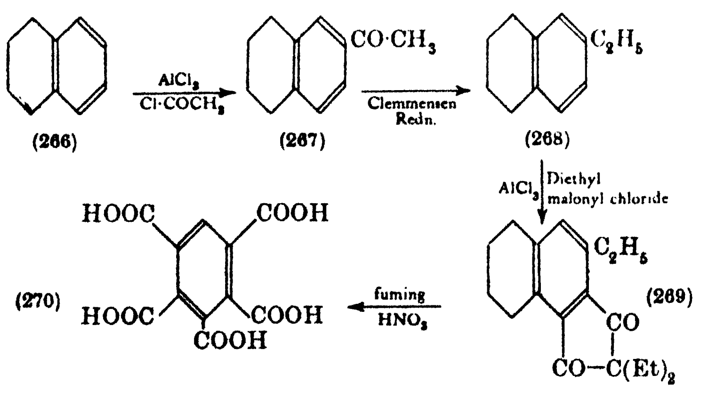


(265)

Benzene Pentacarboxylic Acid.—This acid frequently appears as an end-product in the oxidative degradation of a variety of organic substances, e.g., ergosterol, cadinene, menthene, abietene, cholesterol, etc. It is also obtained by the action of sulphuric acid at 300° on lignin. It may be obtained by the



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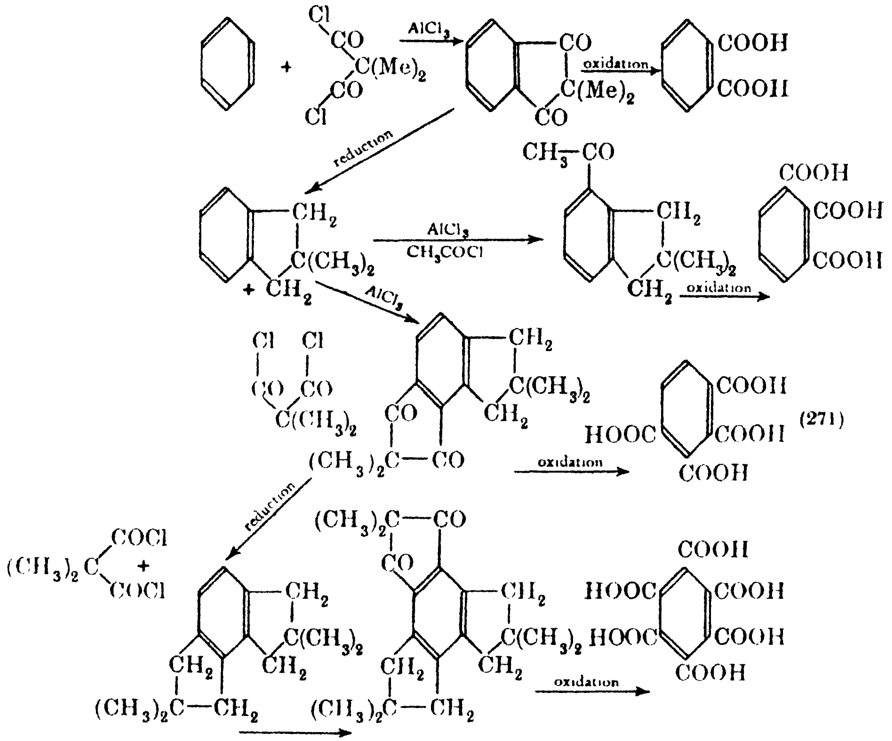
[1] Meyer and Raudnitz, *Ber.*, 1930, **63**, 2010.

[2] Feist, *ibid.*, 1935, **68**, 1941.

oxidation of pentamethylbenzene with permanganate. The easiest method of obtaining benzene pentacarboxylic acid is to carry out the sequence of reactions in the formulæ (266 to 270); producing the required acid (270) *via* the naphthindanedione (269) from tetralin (266).

This method has been extended by Freund [1] to a synthesis of a number of polybasic acids; the reactions by which this has been accomplished are shown in the diagram below :—



(271)

The three benzene tetracarboxylic acids are confused in nomenclature owing to prehnitic acid being a 1, 2, 3, 5- derivative, whereas prehnitene is the vicinal, or 1, 2, 3, 4-tetramethyl benzene. Prehnitic acid (known before the hydrocarbon structure had been worked out) was so named because of its crystallographic similarity to the mineral prehnite (introduced by Col. Pretin, from S. Africa). Its constitution was worked out by Jacobsen,[2] who obtained from it a mono-anhydride, m.p. 239°, and assumed it to be the 1, 2, 3, 4-acid. This, in itself, is a suspicious circumstance, since a tetracarboxylic acid of the 1, 2, 3, 4-configuration would be expected to give a *bis*-anhydride. However, Baeyer [3] had obtained in 1873 mellophanic acid, which had assigned to it, until 1910, the 1, 2, 3, 5- structure; so that two acids were, until 1910, described thus

Prehnitic acid (1, 2, 3, 4-tetra-acid) m. 238–240°.
Mellophanic acid (1, 2, 3, 5-tetra-acid) m. 252–262°.

In 1910, Bamford and Simonsen [4] showed that the two structures should be interchanged; mellophanic acid is the 1, 2, 3, 4-tetracid; prehnitic acid the

---

[1] Freund and Fleischer, *Ann.*, 1916, **411**, 14.

[2] Jacobsen, *Ber.*, 1884, **17**, 2516.

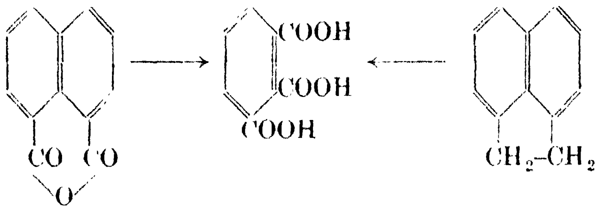
[3] Baeyer, *Ann.*, 1873, **166**, 325.

[4] Bamford and Simonsen, *J.C.S.*, 1910, **97**, 1904.

1, 2, 3, 5-acid. This has been confirmed by Freund's synthesis of mellophanic acid (271) (Table XXX), which *must* give the *vicinal* acid. Further confirmation is derived from the work of Smith and Byrteit.[1]

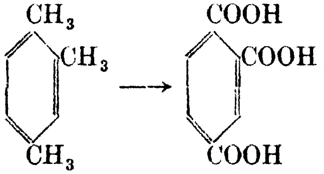
No doubt has assailed our concept of the structure of pyromellitic acid which is firmly established as benzene 1, 2, 4, 5-tetracarboxylic acid. It is obtained when mellitic acid is heated, and as the end-product of a number of degradations by oxidation. Curiously, it is best prepared, although in small yield, by heating willow charcoal with sulphuric acid of 82–88 per cent. strength to 300° in the presence of a little mercury which acts as a catalyst.[2]

The benzene tricarboxylic acids are fairly well known substances: the vicinal hemimellic acid (273) is readily obtained by alkaline permanganate oxidation of naphthalic[3] anhydride (272). Hemimellitene can be used, if available, as a starting material, and recently acenaphthene (274)[4] has been oxidised catalytically to hemimellic acid. It forms a mono-anhydride by simple loss of water on heating.



(272) (273) (274)

The asymmetric, trimellitic acid can be obtained either by the direct permanganate oxidation of ψ-cumene (275) which is industrially available or from the oxidation of resin with nitric acid. On the other hand, the symmetrical trimesic acid is obtained by a large variety of methods, quite apart from the obvious methods of oxidising mesitylene or uvitic acid with permanganate. Thus, numerous derivatives of trimesic acid are obtained, when three molecules of certain aliphatic types react together; as, for example, the formation of trimesic ester from three molecules of formyl acetic ester (276).



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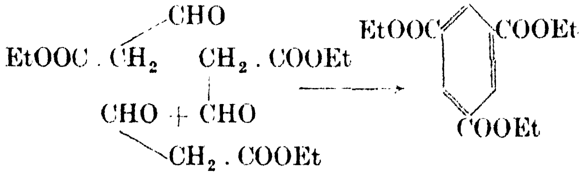


(276)

THE HALOGEN DERIVATIVES OF CARBOXYLIC ACIDS

Halogen substituted Carboxylic Acids

With the exception of the acid fluoride no halides of formic acid have been isolated. The fluoride was obtained by Nesmeyanov and Kahn[5] by the action of a solution of anhydrous formic acid in benzoyl chloride, on potassium fluoride. The acid fluoride (formyl fluoride, H . CO . F) is a gas condensing to a colourless liquid at − 26°. It is very poisonous, and reacts normally as an acid halide to give formanilide with aniline.

---

[1] Smith and Byrteit, *J.A.C.S.*, 1933, **55**, 4305.

[2] Organic Syntheses, 1930, **10**, 90.

[3] Graebe *et al.*, *Ann.*, 1896, **290**, 218; Whitmore and Perkins, *J.A.C.S.*, 1929, **51**, 3352.

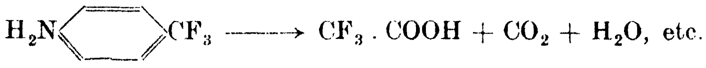
[4] Solden and Jaeger, *Zent.*, 1930, I, 3357; 1932, II, 618; 1933, II, 3050.

[5] Nesmeyanov and Kahn, *Ber.*, 1934, **67**, 372.

As shown in Table *III*, the three fluoroacetic acids, mono-, di- and tri- are all known. They are difficult to obtain, and are best prepared by double decomposition of the corresponding chloro-acid with antimony pentafluoride. This reaction is most successful with the mono-substituted acid :—

$$CH_2Cl\,.\,COOH + SbF_5 \longrightarrow CH_2F\,.\,COOH + SbClF_4$$

The difluoro acid has been made by oxidising the corresponding alcohol, and the trifluoro acid is more easily obtained by oxidising trifluoro-*p*-toluidine with chromic acid—in which process the aromatic ring is destroyed.



The three fluorobenzoic acids are known, and may be obtained by diazotising the appropriate aminobenzoic acid and forming the fluoboric acid salt, which decomposes on heating into the fluorobenzoic acid. In the case of the *m*- and *p*- compound it is sufficient to diazotise in sulphuric acid solution and pour into a very concentrated (70 per cent.) solution of hydrofluoric acid.

Alternatively the fluoroaniline [1] is diazotised and subjected to a cyanide Sandmeyer reaction, thus obtaining the fluorobenzonitrile which can be hydrolysed to the acid.

The properties of some of the halogen substituted acids are given in the summary which follows. Chief among the group, are *mono*-, *di*- and *tri*-chloroacetic acids. Monochloroacetic acid was first prepared by the direct chlorination of acetic acid in the presence of iodine (Leblanc, 1844) [2] and until recently this has been the customary method of making it. The reaction has been the subject of much research, the general conclusion from which is that about 4 per cent. by weight of sulphur is the most satisfactory catalyst for the preparation of monochloroacetic acid. At present the older process has been replaced by two others (*a*) the combination of keten and chlorine to give chloroacetylchloride, which is treated with the theoretical amount of water,

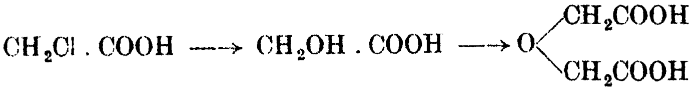
$$CH_2{=}C{=}O + Cl_2 \longrightarrow CH_2Cl\,.\,CO\,.\,Cl \xrightarrow{H_2O} CH_2Cl\,.\,COOH + HCl$$

and (*b*) the interaction of steam and trichloroethylene in the presence of concentrated sulphuric acid, according to the process devised by Simon and Chavanne [3] :—

$$CHCl{=}CCl_2 \longrightarrow CH_2Cl\,.\,COOH + 2HCl$$

Monochloroacetic acid is a crystalline solid with a sharp and penetrating odour, and a strong corrosive action. It is readily soluble in water and has a strong negative heat of solution. Like acetic acid itself, monochloroacetic acid is extremely stable, being decomposed only at a red heat. On the other hand, when solutions of monochloroacetic acid in anhydrous benzene or ether are irradiated, hydrochloric and fumaric acids are formed.

Although monochloroacetic acid is difficult to reduce directly to acetic acid, the chlorine atom is nevertheless quite reactive, being replaced by OH, NH_2, I, CN, etc., with great ease. Chloroacetic acid is quite readily decomposed by boiling with water forming glycollic and diglycollic acids.



$$CH_2Cl\,.\,COOH \longrightarrow CH_2OH\,.\,COOH \longrightarrow O\begin{cases} CH_2COOH \\ CH_2COOH \end{cases}$$

A remarkable reaction of chloroacetic acid is its behaviour with acid potassium fluoride, when fluoroacetic acid and potassium chloride are produced :—

$$2CH_2Cl\,.\,COOH + HKF_2 \longrightarrow 2CH_2F\,.\,COOH + HCl + KCl$$

---

[1] Dyson, *Rec. Trav. Chim.*, 1938, **57**, 1019.

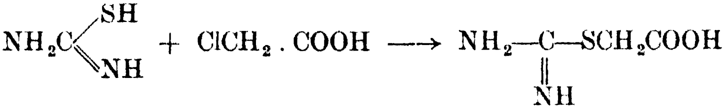
[2] Leblanc, *Ann. Chim. Phys.*, 1844, [3] **10**, 212.

[3] Simon and Chavanne, *C.R.*, 1923, **176**, 309.

This reaction is unusual in its course, but is more remarkable when contrasted with the action of potassium iodide on chloroacetic acid, in which iodacetic acid is obtained :—

$$\mathrm{CH_2Cl\,.\,COOH + KI \longrightarrow CH_2I\,.\,COOH + KCl}$$

The reaction of chloroacetic acid with substances containing the —SH group leads to a variety of useful syntheses. Thus, with thiourea itself, the reaction appears to involve the thiol form, a derivative of pseudothiohydantoic acid being obtained :—



$$\mathrm{NH_2C}\begin{array}{l}\diagup\mathrm{SH}\\ \diagdown\mathrm{NH}\end{array} + \mathrm{ClCH_2\,.\,COOH} \longrightarrow \mathrm{NH_2{-}}\underset{\underset{\mathrm{NH}}{\|}}{\mathrm{C}}\mathrm{{-}SCH_2COOH}$$

With sodium hydrosulphide, thioglycollic acid is obtained :—

$$\mathrm{NaSH + ClCH_2\,.\,COOH \longrightarrow HS\,.\,CH_2\,.\,COOH}$$

With potassium cyanide, chloroacetic acid reacts readily, giving cyanacetic acid :—

$$\mathrm{KCN + Cl\,.\,CH_2COOH \longrightarrow CN\,.\,CH_2\,.\,COOH + KCl}$$

This acid and its ester are extremely important intermediates for the synthesis of aliphatic and alicyclic compounds (see Appendix II).

Potassium nitrite and silver nitrite react readily with chloroacetic acid ; the latter gives nitroacetic acid, $\mathrm{NO_2\,.\,CH_2\,.\,COOH}$, but the former leads to a mixture of substances. The non-ionised portion of the chloro-acid appears to give nitroacetic acid, which breaks down to nitromethane :—

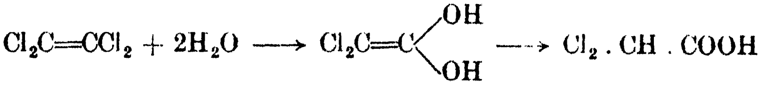
$$\mathrm{Cl\,.\,CH_2\,.\,COOH + KNO_2 \longrightarrow NO_2CH_2COOH \longrightarrow NO_2CH_3 + CO_2}$$

On the other hand, the ionised portion of the chloro-acid gives glycollic acid.

Dichloroacetic Acid.—Although dichloroacetic acid was originally found by Müller[1] in the residues from the preparation of monochloroacetic acid, it is not easily made by the further chlorination of that acid. Until recently the acid has been made, mainly in small quantities for purposes of research, by the reaction of Wallach,[2] in which chloral hydrate is treated with potassium cyanide. The reaction, which follows the course

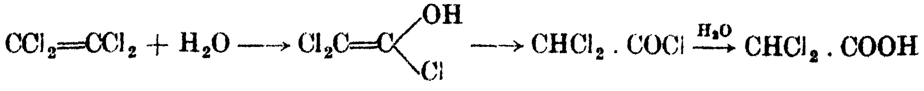
$$\mathrm{CCl_3\,.\,CH(OH)_2 + KCN \longrightarrow CHCl_2\,.\,COOH + KCl + HCN}$$

must be composite, but its precise course has not been elucidated.[3] Recently a variety of methods have been proposed for the manufacture on a large scale. They include the partial decomposition of tetrachloroethylene with steam in the presence of sulphuric acid :—



$$\mathrm{Cl_2C{=}CCl_2 + 2H_2O \longrightarrow Cl_2C{=}C}\begin{array}{l}\diagup\mathrm{OH}\\ \diagdown\mathrm{OH}\end{array} \longrightarrow \mathrm{Cl_2\,.\,CH\,.\,COOH}$$

It is, however, difficult to stop the reaction at this stage, and by using a lower quantity of steam the acid chloride can be obtained in better yield ; this, with the theoretical amount of water, yields the acid :—



$$\mathrm{CCl_2{=}CCl_2 + H_2O \longrightarrow Cl_2C{=}C}\begin{array}{l}\diagup\mathrm{OH}\\ \diagdown\mathrm{Cl}\end{array} \longrightarrow \mathrm{CHCl_2\,.\,COCl \xrightarrow{H_2O} CHCl_2\,.\,COOH}$$

---

[1] Müller, *J.C.S.*, 1864, **17**, 398.

[2] Wallach, *Ber.*, 1873, **6**, 114.

[3] Pücher, *J.A.C.S.*, 1920, **42**, 2251.

Pentachloroethane gives the same final product, when hydrolysed by steam in the presence of sulphuric acid :—

$$CHCl_2 . CCl_3 \xrightarrow{2H_2O} CHCl_2 . COOH + 3HCl$$

The former method, from tetrachloroethylene, is preferable, since by introducing the dichloroacetyl chloride into a column with acetic acid, dichloroacetic acid can be taken off at the foot and acetyl chloride at the head :—

$$CHCl_2 . COCl + CH_3 . COOH \longrightarrow CHCl_2COOH + CH_3 . COCl$$

Dichloroacetic acid is usually met with as a liquid ; a relatively strong acid, which inflicts extremely painful burns. It is far less stable than acetic and monochloroacetic acids, being decomposed at 200–300°.[1] The chlorine atoms are very reactive, and by passing hydrogen into a solution of potassium dichloroacetate containing palladium in suspension, quantitative removal of the chlorine can be achieved. In sunlight, or under ultraviolet irradiation, glyoxylic acid is obtained ; indeed, the heating of dichloroacetic acid with aqueous baryta in an autoclave is one of the best ways of obtaining glyoxylic acid.

$$CHCl_2 . COOH + Ba(OH)_2 \longrightarrow CHO . COOH + BaCl_2 + H_2O$$

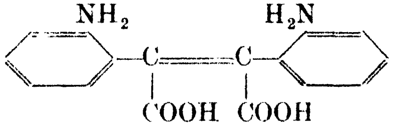
Dichloroacetic acid offers another simple approach to glyoxylic acid, being converted by hydroxylamine to the oxime of the latter compound [2]

$$HONH_2 + CHCl_2 . COOH \longrightarrow HON{=}CH . COOH \longrightarrow CHO . COOH$$

An ingenious modification of this reaction is the process of Swarts [3] in which dichloracetic ester is allowed to react upon potassium fluoride and silica

$$2CHCl_2 . COOEt + SiO_2 + 4KF \longrightarrow 2CHO . COOEt + SiF_4 + 4KCl$$

The reaction of dichloroacetic acid and aniline is anomalous, and constitutes an important method of synthesis of the stilbene series. The reaction proceeds with the formation of a di-*ortho* amino stilbene dicarboxylic acid (277)



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Trichloroacetic acid was discovered by Dumas in 1838, by chlorinating acetic acid.[4] The laboratory preparation of trichloroacetic acid is conducted by oxidation of the corresponding aldehyde, chloral, with nitric acid :—

$$CCl_3CHO + O \longrightarrow CCl_3 . COOH$$

It remains as the main constituent of the residues from the distillation of monochloracetic acid, and is prepared industrially from the acid chloride, itself obtained from tetrachloroethylene and air :—

$$CCl_2{=}CCl_2 \xrightarrow{+O} CCl_3 . COCl \xrightarrow{H_2O} CCl_3 . COOH$$

It is used, industrially, as a source of chloroform which is formed from it by distillation with slightly superheated steam.

Like dichloracetic acid, trichloroacetic acid is easily decomposed by heat, although the course of the decomposition is unusual :—

$$CCl_3 . COOH \longrightarrow COCl_2 + HCl + CO$$

differing entirely from its decomposition in the presence of water or alkalies to form chloroform and carbon dioxide. It is this latter decomposition which makes it an excellent substitute for chloroform in the Reimer-Tiemann synthesis of hydroxyaldehydes.

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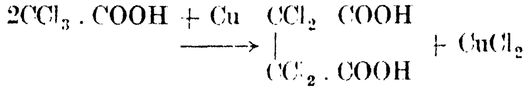
[1] Sonderens, *C.R.*, 1921, **172**, 155.

[2] Hantzsch and Wild, *Ann.*, 1896, **289**, 294.

[3] Swarts, *Chem. Zentr.*, 1903, I, 14.

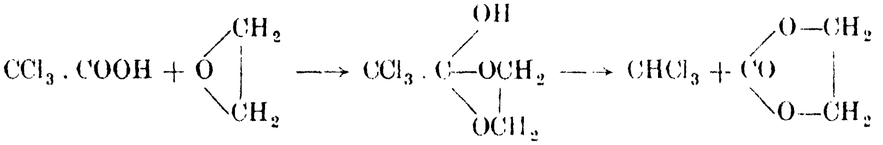
[4] Dumas, *C.R.*, 1839, **8**, 609 ; *Ann.*, 1839, **32**, 101.

Trichloroacetic acid is readily reduced to acetic acid by strong reducing agents such as hydrogen and palladium or concentrated hydriodic acid at 100°. Less active agents reduce it to dichloro- or monochloroacetic acid. An interesting modification of this reduction is the formation of tetrachlorosuccinic acid by the reduction of two molecules of trichloroacetic acid in ethereal solution by copper powder [1]



$$2CCl_3 . COOH + Cu \longrightarrow \begin{array}{l} CCl_2 . COOH \\ | \\ CCl_2 . COOH \end{array} + CuCl_2$$

The carboxyl group of trichloroacetic acid is undoubtedly abnormal, as Meerwein [2] has shown it to give a reaction with ethylene oxide leading to a cyclic acetal (278) which readily decomposes on warming in neutral, acid or



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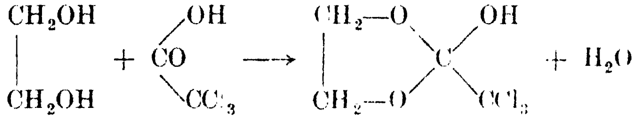
alkaline solutions to give ethylene glycol carbonate. Again, trichloroacetic acid shows abnormal esterification, yielding a cyclic *ortho*-carbonic derivative with ethylene glycol.



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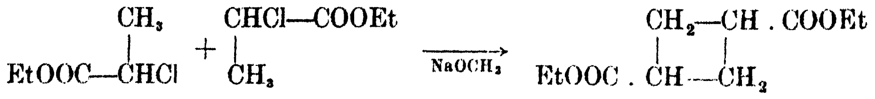
α-Chloropropionic acid.—The most economical method of preparing this acid is by the action of thionyl chloride on anhydrous lactic acid.

$$CH_3CH(OH)COOH + SOCl_2 \longrightarrow CH_3 . CHCl . COOH + SO_2 + HCl$$

The residue, on vacuum distillation, gives α-chloropropionic acid in fairly good yield. The chlorination of propionic acid gives almost exclusively the α-monochloro derivative, and an additional method is condensation of aldehyde and hydrocyanic acid to give the nitrile of lactic acid, which is converted to α-chloropropionic acid by the reactions indicated below :—

$$CH_3CHO + HCN \longrightarrow CH_3 . CH(OH)CN \xrightarrow{SOCl_2} CH_3 . CHCl . CN$$
$$\xrightarrow{HCl} CH_3 . CHCl . COOH$$

There are few properties of α-monochloropropionic acid which make it notable, but it may be noted that, on treatment with sodium methoxide, the ester furnishes a useful approach to the *cyclo*-butane series, giving a mixture of *cis*- and *trans-cyclo*-butane dicarboxylic ester :—



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[1] Dumas, *C.R.*, 1839, **8**, 609 ; *Ann.*, 1839, **32**, 101.

[2] Meerwein and Hinz, *ibid.*, 1931, **484**, 1.

TABLE XXXI

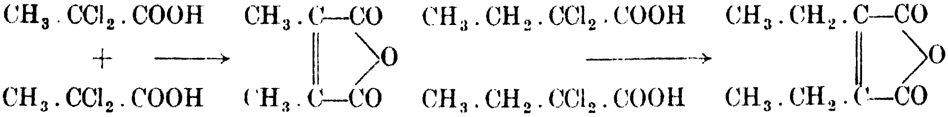
SOME HALOGEN-SUBSTITUTED ALIPHATIC ACIDS

Acid	m.	b.	d.	K
Fluoroacetic	+ 33°	165°	—	$0{\cdot}218 \times 10^{-2}$
Difluoroacetic	− 0·35°	134°	$1{\cdot}5359^{10}$	$5{\cdot}74 \times 10^{-2}$
Trifluoroacetic	− 15°	72°	—	50×10^{-2}
Chloroacetic α-	62°	189°	—	$1{\cdot}5 \times 10^{-3}$
,, β-	50°			
Dichloroacetic α-	+ 10°	192°	$1{\cdot}5657^{20}_{4}$	5×10^{-2}
,, β-	− 4·1°			
Trichloroacetic	58°	195°	—	20×10^{-2}
Bromoacetic	49°	196°	$1{\cdot}9335^{50}_{50}$	$0{\cdot}2 \times 10^{-2}$
Dibromoacetic	—	232–234°	—	$8{\cdot}1 \times 10^{-2}$
Tribromoacetic	131°	245°	—	—
Iodoacetic	82°	—	—	$7{\cdot}5 \times 10^{-4}$
Di-iodoacetic	95–96°	—	—	—
Tri-iodoacetic	d. 150°	—	—	—
α-Chloropropionic	—	186°	1·306	$1{\cdot}465 \times 10^{-3}$
β-Chloropropionic	39°	204°	—	$0{\cdot}086 \times 10^{-3}$
αα-Dichloropropionic	—	185–190°	—	—
α-Bromopropionic-*l*	− 0·5°	—	—	—
,, -*dl*	+ 25·7° − 4°	95–96°/10 mm.	$1{\cdot}700^{20}_{4}$	$1{\cdot}08 \times 10^{-3}$
β-Bromopropionic	62°	—	—	$0{\cdot}098 \times 10^{-3}$
αα-Dibromopropionic	61°	126°/29 mm.	—	33×10^{-3}
αβ-Dibromopropionic α-	64°	-	—	—
,, β-	51°			
α-Iodopropionic	45·5°	105°/0·3 mm.	—	$[\alpha]_D^{20} \pm 82{\cdot}5°$
Pentachloropropionic	decomp.	—	-	0·3
α-Chlorobutyric	—	101°/15 mm.	-	$1{\cdot}39 \times 10^{-3}$
β-Chlorobutyric *d*-	43–44·5°	101°/13 mm.	·	$[\alpha]_D^{20} = + 49{\cdot}8°$ (H_2O)
,, *l*-	—	—	-	$[\alpha]_D^{20} = - 33{\cdot}4°$ (toluene)
,, *dl*-	16–16·5°	108–109°/17 mm.	$1{\cdot}1898^{20}_{4}$	$0{\cdot}089 \times 10^{-3}$
γ-Chlorobutyric	16°	115°/16 mm.	$1{\cdot}2236^{20}_{4}$	$0{\cdot}03 \times 10^{-3}$
αβ-Dichlorobutyric α-	63°	124°/20 mm.	—	$8{\cdot}2 \times 10^{-3}$
,, β-	78°	131·5°/20 mm.	—	$6{\cdot}1 \times 10^{-3}$
α-Bromobutyric	− 4°	114–115°/20 mm.	$1{\cdot}5735^{13}_{15}$	$1{\cdot}06 \times 10^{-3}$
β-Bromobutyric	17–18°	122°/16 mm.	—	—
γ-Bromobutyric	32–33°	—	—	$0{\cdot}026 \times 10^{-3}$
α-Iodobutyric	41–42°	—	—	—
γ-Iodobutyric	40–41°	—	—	$0{\cdot}023 \times 10^{-3}$
α-Chloroacrylic	65°	—	—	—
β-Chloroacrylic α-	84–85°	—	—	$2{\cdot}2 \times 10^{-4}$
,, β-	63–64°	—	—	$4{\cdot}7 \times 10^{-4}$
αβ-Dichloroacrylic	85–86°	—	—	—
Trichloroacrylic	76°	—	—	7×10^{-2}
α-Bromoacrylic	69–70°	—	—	—
β-Bromoacrylic	115–116°	—	—	—
αβ-Dibromoacrylic	85–86°	—	—	—
ββ-Dibromoacrylic	85–86°	—	—	—
Tribromoacrylic	118°	—	—	—
Tri-iodoacrylic	207°	—	—	—
α-Chlorocrotonic	—	103–104°/19 mm.	$1{\cdot}237^{22}$	—
β-Chloropropiolic	69–70°	—	—	—
β-Bromopropiolic	84–85°	—	—	—
β-Iodopropiolic	142°	—	—	—

The β-chloroacid is usually prepared by the addition of hydrogen chloride to acrolein, and the oxidation of β-chloropropionaldehyde so formed. The deviation from Markownikov's rule is to be noted.

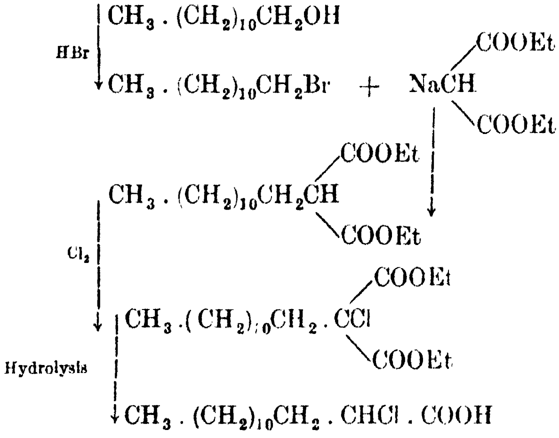
$$CH_2{=}CH\,.\,CHO + HCl \xrightarrow{\qquad} CH_2Cl\,.\,CH_2\,.\,CHO \xrightarrow{\text{oxidation}} CH_2Cl\,.\,CH_2\,.\,COOH$$

There are several dichloropropionic acids known, of which the αα-dichloro acid is the most valuable. When αα-dichloropropionic or αα-dichlorobutyric acid is treated with silver powder in benzene solution [1] substituted maleic anhydrides are formed. These can be converted to the corresponding imides which are of great value in identifying the pyrrole fragments from plant and blood pigments. The acid corresponding to the diethyl derivative was termed 'xeronic acid' (from ξηρος = dry, an allusion to its extreme tendency to pass into its anhydride (279*a*)). The α, β-dichloropropionic acid may be obtained by addition of chlorine to acrylic acid or to acrolein followed by oxidation.



(279*a*)

There are very few of the higher chloro-acids which call for individual comment; many of them may be obtained by the general method of adding chlorine to certain of the naturally occurring unsaturated acids, as for example, 9, 10-dichloro-octadecane acid by the cautious addition of chlorine to oleic acid. The higher fatty acids take up chlorine in the α-position, but only very slowly, and the α-chloro acids are best prepared from the higher alcohols by the sequence of reactions :—


CH₃ . (CH₂)₁₀CH₂OH
HBr
CH₃ . (CH₂)₁₀CH₂Br + NaCH(COOEt)₂
CH₃ . (CH₂)₁₀CH₂CH(COOEt)₂
Cl₂
CH₃ . (CH₂)₁₀CH₂ . CCl(COOEt)₂
Hydrolysis
CH₃ . (CH₂)₁₀CH₂ . CHCl . COOH

It is difficult to synthesise chloro acids in which the halogen occupies a place between the α- and ω- positions; the ω-chloro acids are, however, obtained comparatively easily; the procedures are shown in the scheme at the top of opposite page.

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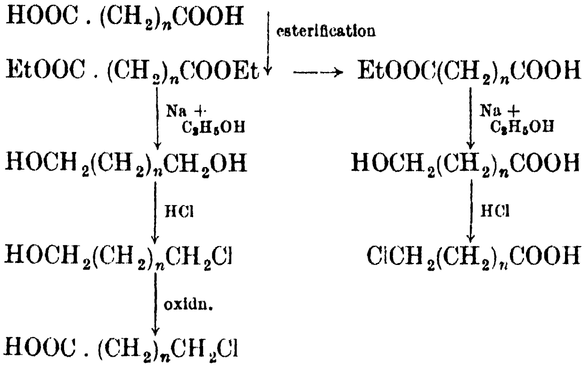
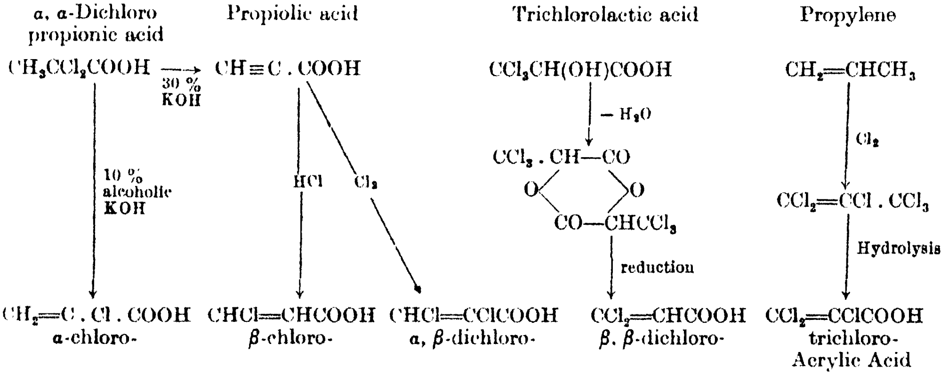
[1] Holst, *J. Pr. Chem.*, 1890, 2 **41**, 461. Beckerts and Otto, *Ber.*, 1885, **18**, 836.



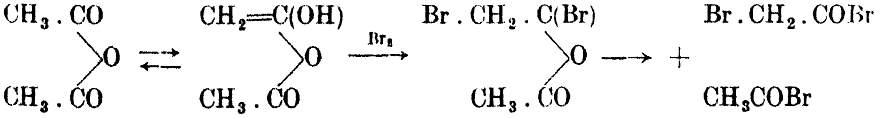
UNSATURATED CHLORO-ACIDS

All possible mono-, di- and trichloro derivatives of acrylic acid have been prepared ; the general methods of obtaining them are shown in the diagram below, the main points of interest being the partial removal of hydrochloric acid from α, α-dichloropropionic acid to give α-chloroacrylic acid and the use of hexachloro propylene.



Few, if any, of the higher chloro-unsaturated acids call for comment, and it is proposed to proceed to a consideration of bromo- acids.

Aliphatic Bromo-acids.—The direct bromination of acetic acid, even in the presence of catalysts is slow,[1] and the best method of obtaining the bromo-acid is by the bromination of a mixture of acetic anhydride and acetic acid with bromine which has been completely freed from water by agitation with concentrated sulphuric acid. The course of the action appears to be *via* the enol form of the anhydride (280). This instantaneously adds bromine to give



(280) (281) (282)

the hypothetical intermediate (281) which breaks down to bromoacetyl bromide and acetyl bromide (287). The latter reacts with the acetic acid present to regenerate acetic anhydride.

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[1] Perkin and Duppa, *J.C.S.*, 1857, **11**, 22 and 1859, **12**, 1.

The direct addition of bromine to keten is a reaction which appears capable

$$Br_2 + CH_2{=}C{=}O \longrightarrow CH_2Br.COBr$$

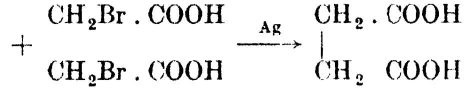
of providing a means of obtaining bromoacetic acid cheaply; the reaction is somewhat complicated by the fact that during the period of time necessary for the formation of bromoacetyl bromide some dimerisation of the keten takes place, and the product will, therefore, contain some derivatives of α-bromo acetoacetyl bromide. It is probable that the aerial oxidation of 1, 1-dibromoethylene to bromoacetyl bromide, observed by Demole in 1878 [1] is due to the formation of keten and its immediate bromination :—

$$CH_2{=}CBr_2 + O \longrightarrow CH_2{=}CO + Br_2 \longrightarrow CH_2Br.COBr$$

Bromoacetic acid, a solid, m. 49–50°, boils, with only slight decomposition at 208°. It causes deep and painful burns, which heal slowly.

Chemically, bromoacetic acid is very reactive; in sunlight and even at the temperature of liquid air, it decomposes with the liberation of elementary bromine. In the presence of palladium and hydrogen the bromine is removed quantitatively.[3]

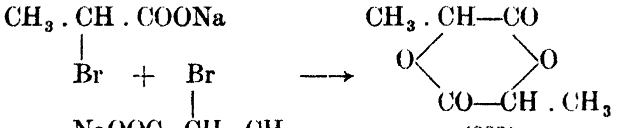
The decomposition with silver powder to succinic acid is complete at 130°. With water, glycollic and diglycollic acids are obtained.



$$\begin{array}{l}CH_2Br.COOH\\ +\\ CH_2Br.COOH\end{array}\xrightarrow{Ag}\begin{array}{l}CH_2.COOH\\ |\\ CH_2\ \ COOH\end{array}$$

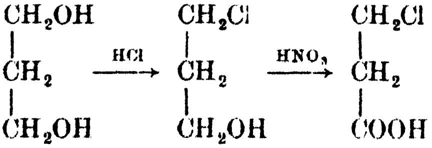
Di- and tri-bromoacetic acids are not frequently encountered. The former is obtained by the persistent bromination of a mixture of acetic acid and acetic anhydride [2] in the presence of ultraviolet light, and the latter by the nitric acid oxidation of bromal. It is also obtained by the bromination of malonic acid. The reactions of these two acids are entirely analogous to those of the corresponding chloro acids.

α-Bromopropionic acid may be obtained by the direct bromination of propionic acid, and is characterised by the extreme lability of the α-bromine, which is completely hydrolysed by warm water giving lactic acid. The relation between lactic and α-bromopropionic acids is emphasised by the formation of lactide (283) when the sodium salt of the latter is distilled.



(283)

β-Bromopropionic acid may be obtained, although only in moderate yield, from the addition of hydrogen bromide to acrylic acid. Practically, it is best prepared from trimethylene glycol, by conversion to the chlorhydrin and oxidation with nitric acid.



$$\begin{array}{l}CH_2OH\\ |\\ CH_2\\ |\\ CH_2OH\end{array}\xrightarrow{HCl}\begin{array}{l}CH_2Cl\\ |\\ CH_2\\ |\\ CH_2OH\end{array}\xrightarrow{HNO_3}\begin{array}{l}CH_2Cl\\ |\\ CH_2\\ |\\ COOH\end{array}$$

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[1] Demole, *Ber.*, 1878, **11**, 1307.

[2] Shaw, *J.C.S.*, 1923, **123**, 2233.

[3] Brusch and Stobe, *Ber.*, 1916, **49**, 1371.

The halogen is not so labile as that in the α-position, and derivatives are not so easily prepared. On the other hand, the α, β-dichloropropionic acid (made by the addition of chlorine to acrylic acid) shows a greater reactivity in respect of its β-halogen atom, than the α-, as also does the corresponding α, β-dibromo acid. Thus, with mild alkalies the β-hydroxy-α-bromopropionic acid is formed, whilst on autoclaving the acid with ammonia *iso*-serine is obtained

$$\begin{tikzcd}
HOCH_2 . CHBr . COOH \\
CH_2Br . CHBr . COOH \arrow[u, "Ag_2CO_3"'] \arrow[d, "NH_4OH"] \\
CH_2(NH_2)CHOH . COOH
\end{tikzcd}$$

The higher α-bromoaliphatic acids are all fairly readily prepared by the direct bromination of the acid in the presence of red phosphorus. Thus, α-bromo acids from α-bromobutyric up to α-bromodocosanoic acid (α-bromobehenic acid) have been obtained[1] by this method. The primary product is the α-bromo acid bromide, $CH_3(CH_2)_n . CHBr . COBr$, which is then hydrolysed to the acid.

Aliphatic Iodo-acids

Of these, monoiodoacetic acid is easily the most important. It is not obtained by direct iodination of acetic acid, but by the treatment of chloroacetic acid with a solution of sodium iodide in acetone. Double decomposition rapidly ensues, and the sodium chloride, being insoluble in acetone, is precipitated. It is then easy to recover the iodoacetic acid from the acetone solution by evaporation. Monoiodoacetic acid is a crystalline solid, m. 82°, with a marked lachrymatory action.

The reaction just described for iodo-acetic acid is general for α-iodoaliphatic acids and is used for their preparation. One or two of the iodo aliphatic acids have a biochemical application. Lundsgaard in 1929[2] showed that sodium iodoacetate inhibited the formation of muscle-lactic acid without affecting the contractile power of the tissue.

The calcium salt of α-iodobehenic acid is used therapeutically under the names 'Sajodin', or 'Caliben', and di-iodotariric acid ('Iodostarin') is also used in medicine.

In the previous section no reference has been made to halogen derivatives of dibasic acids. Monochloromalonic ester may be obtained by bubbling chlorine through an ethereal dilution of malonic ester until the theoretical weight has been used; after which the acid itself may be obtained by hydrolysis. It is a crystalline substance, m. 133°, which is of value as a synthetic agent. The dichloro acid may be obtained by the direct chlorination of malonic acid with two molecular proportions of sulphuryl chloride in ether. The corresponding bromo acids are known.

The halogen derivatives of succinic acid have been carefully studied in connexion with the Walden inversion (see Vol. III). The mono halogen derivatives may be obtained by addition of halogen acid to maleic or fumaric acids, or by the action of phosphorus pentahalide on malic acid. The properties of the acids are given in Table XXXII. The dichloro acids may be obtained by a variety of reactions which are shown in the diagram below. It will be observed from this diagram that it is not always easy to predict the stereochemical course of a simple reaction.

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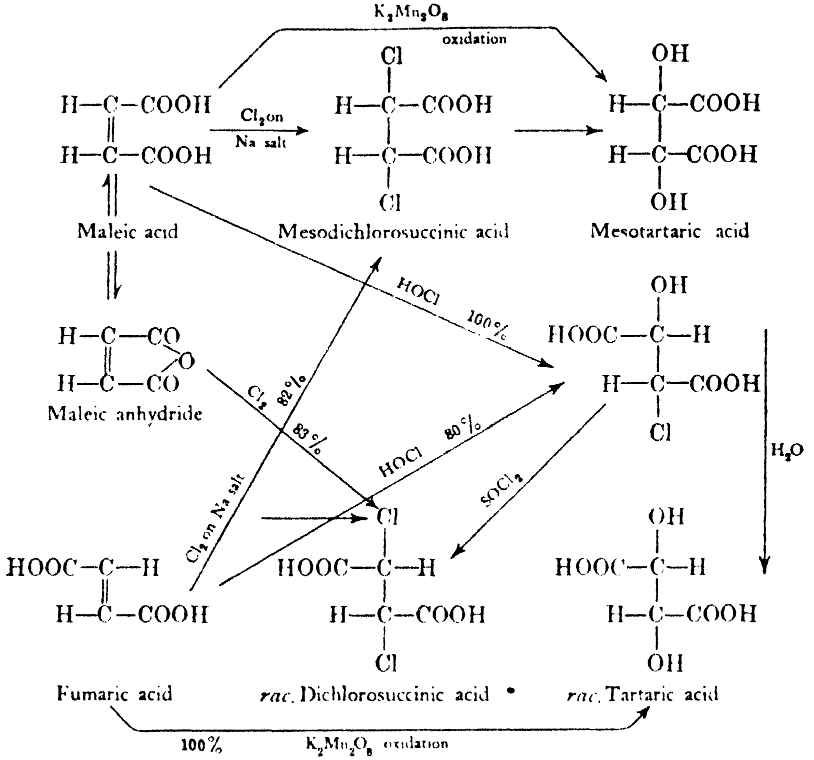
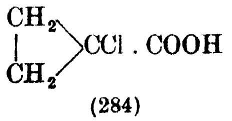
[1] Baczewski, *Monats.*, 1896, **17**, 530.

[2] Lundsgaard, *Biochem. Z.*, 1930, **217**, 162.



Alicyclic and Aromatic Halogeno-acids

A number of the halogen substituted acids of the *cyclo*propane series is known ; some 1-chloro*cyclo*propane carboxylic acid (284) can be obtained by direct chlorination, and the corresponding *cyclo*butane derivative (285) is also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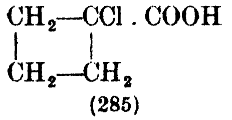
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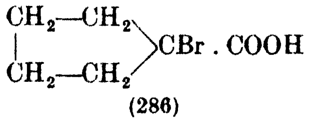

(286)

obtainable by direct chlorination in the presence of red phosphorus. The reaction appears to be general, and may be extended to the *cyclo*pentane series by the action of bromine and phosphorus pentabromide on the acid ; this gives the α-bromo*cyclo*pentyl carboxylic acid bromide which may be hydrolysed by aqueous methyl alcohol to the corresponding acid (286).

The *cyclo*hexane carboxylic acids are better known than any others of this series, and may be obtained (1) by the addition of hydrogen bromide to the various *cyclo*hexene carboxylic acids ; (2) in the case of the α-chloro acid the general method above may be used ; and (3) by the action of hydrobromic acid on the corresponding hydroxy acids, obtained by catalytic reduction of the various hydroxy benzoic acids.

TABLE XXXII

Some Halogenated Dibasic Acids

Acid	Properties			
Chloromalonic	m. 133°. $K_1 = 4 \times 10^{-2}$; $K_2 = 194 \times 10^{-6}$			
Bromomalonic	m. 113°.			
Dichloromalonic	Liquid. Decomp. on boiling at 760 mm.			
Dibromomalonic	m. 147°			
	Racemic	Dextro	Lævo	Meso
Monochlorosuccinic	m. 153–154° $K_1 = 2{\cdot}84 \times 10^{-3}$ m.p. anhydride 40–41° —	176° $K_1 = 2{\cdot}94 \times 10^{-3}$ m.p. anhydride 80° $[\alpha]_D^{18\cdot5} = +\ 20{\cdot}1°$	176° $K_1 = 2{\cdot}94 \times 10^{-3}$ — $[\alpha]_D^{14} = -\ 18{\cdot}92°$	
Monobromosuccinic	m. 163° $K_1 = 2{\cdot}68 \times 10^{-3}$ m.p. anhydride 30–31° —	173° — — $[\alpha]_D^{15} = +\ 41{\cdot}9°$	179° $K_1 = 2{\cdot}68 \times 10^{-3}$ — $[\alpha]_D^{20} = -\ 70{\cdot}2°$ (in EtAc)	
Mono-iodosuccinic	m. 135–140° —	150–152° $[\alpha]_D^{19} = -\ 54{\cdot}9°$	— —	
Dichlorosuccinic	m. 175° $K_1 = 37{\cdot}2 \times 10^{-3}$ $K_2 = 18 \times 10^{-4}$ —	166–167° — — $[\alpha]_D^{25} = +\ 80{\cdot}41°$	166–167° — — $[\alpha]_D^{25} = -\ 80{\cdot}38°$	217–218° $K_1 = 36{\cdot}1 \times 10^{-3}$, $K_2 = 9{\cdot}4 \times 10^{-4}$ — —
Dibromosuccinic	m. 169–170° $K_1 = 41{\cdot}5 \times 10^{-3}$ $K_2 = 8{\cdot}17 \times 10^{-4}$ —	151–153° — — $[\alpha]_D^{15}$ + 126·3°	157–158° — — $[\alpha]_D^{15} = -\ 148°$	257° $K_1 = 35{\cdot}7 \times 10^{-3}$, $K_2 = 23{\cdot}9 \times 10^{-4}$ — —

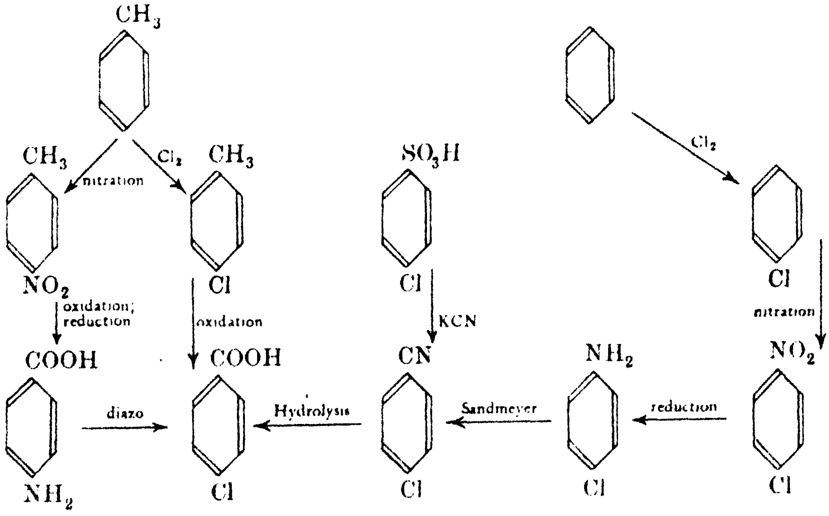
The hexachloro derivative is obtained from the direct chlorination of benzoyl chloride under insolation. The physical properties of some of the better known acids of this series are shown in Table XXXIII.

TABLE XXXIII

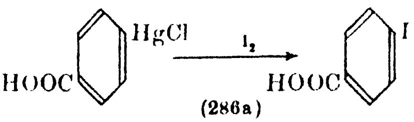
Some Alicyclic Halogen Substituted Acids

Carboxylic acid	M.P.	B.P.
1-Bromo-*cyclo*propane	70-71°	—
1-Bromo-*cyclo*butane	85°	—
1-Bromo-*cyclo*pentane	122-125°	—
1-Bromo-*cyclo*hexane	63°	125-127°/25 mm.
2-Bromo-*cyclo*hexane	108-109°	—
3-Bromo-*cyclo*-hexane	*cis*- 62-63°	—
	trans- 167°	—
4-Bromo-*cyclo*hexane	160-167°	—
1, 2, 3, 4, 5, 6-Hexachloro-*cyclo*hexane	236°	—
1-Chloro-*cyclo*hexane	89-90°	—
1-Bromo-*cyclo*heptane	89-91°	—
1-Chloro-*cyclo*heptane	42-44°	—
2-Bromo-*cyclo*heptane	—	167-168°/12 mm.

There are various methods by which the halogen substituted benzoic acids can be prepared; direct halogenation is seldom successful, and scarcely ever used. The main methods are set out in the diagram below in which *p*-chlorobenzoic acid has been taken as an example :—



These reactions take place in a comparatively straightforward manner with most of the halogens—most difficulty being encountered with iodine substituted compounds. There are, however, alternative methods of producing iodo derivatives, such as the action of iodine on 4-chloromercuribenzoic acid (286a). A corresponding method from the anhydro-*ortho* mercuribenzoic acid is available for the preparation of *o*-iodobenzoic acid (287). The *m*-iodo acid is obtained by the action of potassium iodate on benzoic acid dissolved in sulphuric acid. This latter reaction is exactly parallel to an old method due to Wroblewski[1] for preparing the *m*-chloro acid from benzoic acid, potassium chlorate and hydrochloric acid.



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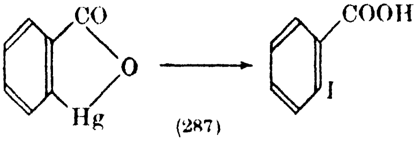
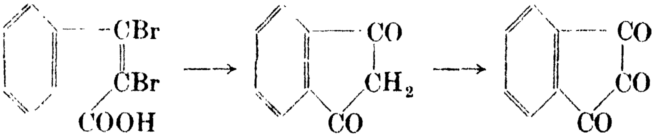


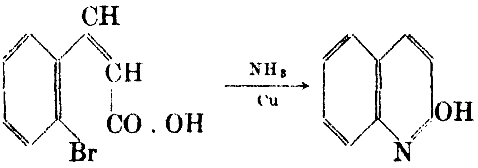
(287)

The most interesting members of the series appear to be the halogen derivatives of cinnamic acid. The α, β-dibromo compound on treatment with concentrated sulphuric acid gives an indene derivative, and on warming the solution, indanedione-1, 3 (288) is formed. This has an active methylene group and will react through its sodio derivative. It may be oxidised to ninhydrin or triketohydrindene (289), the hydrate of which is used in biochemical analysis for detecting amino- acids, etc., with which it gives a blue colour.



(288) (289)

o-Bromocinnamic acid can be used as an approach to the quinoline series since on heating with ammonia in the presence of copper at 180° it yields 2-hydroxyquinoline (290).



(290)

Monohydroxy Aliphatic Acids

It is not proposed to treat carbonic acid, HO . COOH, as a member of this series, but to commence this section with glycollic acid. This substance derives its name from Strecker's original preparation[2] in 1848; glycine (aminoacetic acid)—or as it was then called 'glycocoll'—was subjected to the action of nitrous acid, glycollic acid being the result. Glycollic acid occurs naturally in grapes (unripe) and the leaves of Virginia creeper, and may be prepared by a large variety of reactions, some of which are summarised in Table XXXV.

[1] Wroblewski, *Ann.*, 1873, **168**, 200.
[2] Strecker, *ibid.*, 1848, **68**, 55.

TABLE XXXIV

SOME HALOGENATED AROMATIC ACIDS

ACID	Position of substituents	SUBSTITUENT			
		F	Cl	Br	I
Mono - benzoic	2	m. 126° $K = 30 \times 10^{-5}$	m. 140° $K = 130 \times 10^{-5}$	m. 149° $K = 140\text{–}180 \times 10^{-5}$	m. 162° $K = 140 \times 10^{-5}$
Mono - benzoic	3	m. 124° $K = 14 \times 10^{-5}$	m. 156° $K = 150 \times 10^{-5}$	m. 155° $K = 15 \times 10^{-5}$	m. 187–188° $K = 1{\cdot}6 \times 10^{-5}$
Mono - benzoic	4	m. 182° $K = 14 \times 10^{-5}$	m. 239° $K = 70 \times 10^{-5}$	m. 250–254°	m. 267°
Di - benzoic	2, 3	—	m. 163°	m. 149–150°	—
Di - benzoic	2, 4	—	m. 160°	m. 168–173°	m. 169–170°
Di - benzoic	2, 5	—	m. 153°	m. 153°	m. 183°
Di - benzoic	2, 6	—	m. 139°	m. 146–147°	—
Di - benzoic	3, 4	—	m. 204°	m. 234–235°	m. 257°
Di - benzoic	3, 5	—	m. 188°	m. 213–219°	m. 235°
Tri - benzoic	2, 3, 4	—	m. 186–187°	m. 197–198°	—
Tri - benzoic	2, 3, 5	—	m. 162°	m. 193–194°	—
Tri - benzoic	2, 4, 5	—	m. 162–164°	—	—
Tri - benzoic	2, 4, 6	—	m. 160–161°	m. 186–187°	—

Tri – benzoic	3, 4, 5			m. 203°		m. 235°		—	
Tetra – benzoic	2, 3, 4, 5	—		m. 186°		—		—	
Penta – benzoic	2, 3, 4, 5, 6	—		m. 201°		m. 252°		—	
Mono – phenylacetic	α- . *d*- α- . *dl*-	— —		m. 60–61° m. 78° K = 440 × 10^{-5}		m. 76–78° m. 83° K = 350 × 10^{-5}		—	
Mono – phenylacetic	4-	—		m. 105–106° K = 6·4 × 10^{-5}		m. 114–115° K = 6·4 × 10^{-5}		m. 135° K = 6·6 × 10^{-5}	
		cis-	*trans-*	*cis-*	*trans-*	*cis-*	*trans-*	*cis-*	*trans-*
Mono – cinnamic	α-	— —	m. 157° —	m. 111° K, 1070	m. 138–9° K, 97	m. 131° K, 1440	m. 120–1° K, 93	m. 111° —	m. 130° —
Mono – cinnamic	β-	— —	— —	m. 132·5° K, 27	m. 140° K, 28	m. 160° —	m. 135° —	m. 188° —	m. 128° K, 40
Di – cinnamic	α, β-	—	—	m. 121°	m. 101°	m. 100°	m. 137°	—	m. 171°
Mono – cinnamic	2	—	—	m. 127°	m. 211°	—	—	—	—
Mono – phenyl-propiolic	2	—		m. 131°		m. 118°		—	
Mono – phenyl-propiolic	3	—		m. 140°		m. 135°		—	
Mono – phenyl-propiolic	4	—		m. 160°		—		—	

TABLE XXXV

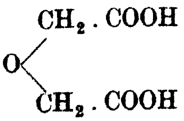
SOME METHODS OF OBTAINING GLYCOLLIC ACID

	Method	Originator	Reference
1.	From the mother liquor remaining after the industrial manufacture of mercury fulminate. This is rich in glycollic acid which may be recovered after removal of any mercury with H_2S	First observed by Clöez; applied by Fahlberg	*Ann.*, 1852, **84**, 282 *J. Pr. Chem.*, 1836, **7**, 329
2.	The oxidation of alcohol with dilute nitric acid	Discovered by Debus; improved by Lautemann and Drechsel	*Ann.*, 1856, **100**, 1 Kolbe, *Lehrbuch*, Vol. 1, 678 *Ann.*, 1863, **127**, 150
3.	Oxidation of glycol with dilute nitric acid	Würtz	*C.R.*, **44**, 1306
4.	Boiling aqueous solutions of chloroacetic acid, or of potassium chloroacetic	Kekulé Fittig	*Ann.*, 1858, **105**, 286 *Ann.*, 1880, **205**, 191
5.	By boiling invert sugar with chalk and silver oxide in aqueous suspension. The yield is about 30 % by weight of dry calcium glycollate	Kiliani	*Ann.*, 1880, **205**, 191
6.	The hydrolysis of the potassium carbonyl obtained from carbon monoxide on passage through metallic potassium dissolved in liquid ammonia	Joannis	*C.R.* 1914, **158**, 874
7.	The electrolysis of oxalic acid solution with lead electrodes		

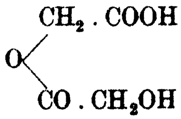
Glycollic acid is difficult to obtain crystalline and dry although it is not hygroscopic; it forms two types of crystals, a stable form, m. 80°, and a labile form, m. 63°. The difficulty of crystallisation lies in the presence of anhydro forms of the acid in its concentrated syrup which delay or inhibit crystallisation.

The combination of alcoholic and acidic structures so near together in the same molecule makes intermolecular reaction of glycollic acid particularly easy. Five substances may be produced by loss of water from glycollic acid

(1) The simple ether, diglycollic acid (291).
(2) The ester (292).
(3) The diglycollic anhydride (293).



(291)



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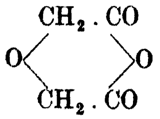

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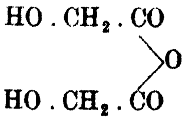

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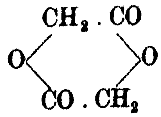


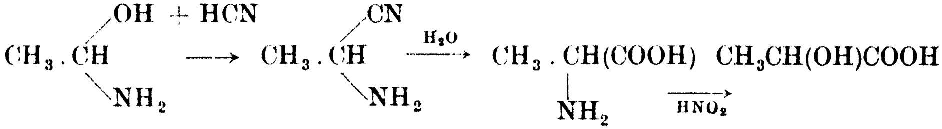
(295)

(4) The cyclic di-ester, glycollide (295).
(5) A large ring polymer of indeterminate structure and molecular weight. (Polyglycollide.)

The simple anhydride (294) does not appear to be capable of existence. When glycollic acid is heated at 100° the ester (292) is first formed and passes on further heating into the polymer, polyglycollide. Diglycollic acid can be obtained by boiling an aqueous solution of the simple acid but is more conveniently obtained by boiling calcium chloroacetate solution with lime. Diglycollic anhydride is obtained by heating diglycollic acid; whilst the glycollide is obtained by distilling sodium bromoacetate in vacuum. No extensive industrial applications of glycollic acid have been made, although its use in dyebaths for printed fabrics has been tried on a semi-industrial scale.

LACTIC ACID

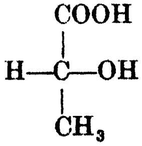
Although Scheele in 1780 [1] isolated lactic acid from sour milk and crystallised its zinc salt, subsequent investigators (Bouillon-Lagrange, Fourcroy and Vauquelin) dismissed the substance as acetic acid which had become contaminated with 'animal matter'. Liebig and Mitscherlich analysed the acid in 1832 and re-established its identity as a new substance; later, in 1847, Liebig showed that the lactic acid of sour milk differed from that of flesh. The first synthesis of lactic acid was that of Strecker,[2] who caused hydrogen cyanide to react with aldehyde ammonia, obtaining alanine thereby (296). This is converted by nitrous acid to lactic acid, which is, of course, optically inactive.



(296)

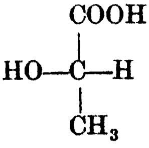
Lactic acid is essentially a fermentation product; there are very few substrates ranging from cabbage stalks to pure sugars which cannot be fermented to lactic acid with a suitable strain of organism. Industrially, cheese-whey has proved an excellent source of lactic acid, as it contains most of the lactose of the original milk and is capable of fermentation by *B. lactis acidi*. Chalk is added to the fermenting liquor to keep it neutral and the material becomes converted in a few days to calcium lactate which serves as the basis for the production of other salts, and of the acid itself. The waste liquor from starch processing can be boiled to hydrolyse the carbohydrate to a mixture of lower sugars which can be fermented to lactic acid by *B. Delbrückii*.

The lactic acid of industry is usually handled in 50 per cent. aqueous solution. The anhydrous D- or L- forms melt at 28°, but the inactive form melts at 18°. The initials D- and L- are used in this chapter conventionally to indicate that the structure of the two lactic acids so denominated is such that in the D-acid the hydroxyl group is at the right when the molecule is drawn as below; and that



$$\begin{array}{c} COOH \\ | \\ H\text{—}C\text{—}OH \\ | \\ CH_3 \end{array}$$

D-lactic acid



$$\begin{array}{c} COOH \\ | \\ HO\text{—}C\text{—}H \\ | \\ CH_3 \end{array}$$

L-lactic acid

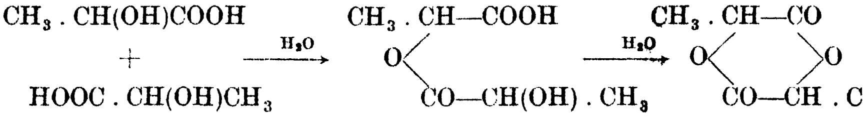
in L-lactic acid the hydroxyl group is to the left; one form is, therefore, the mirror image of the other. This assignment of D- and L- is purely a matter of configuration, and has no relation to the question of nature (*dextro-* or *lævo-*) of the optical rotation of the compound. It so happens in this case that D-lactic acid is *dextro*-rotatory, and that L-lactic acid is *lævo*-rotatory, but the salts and esters of D-lactic acid are *lævo*-rotatory. This very important convention, namely that the labels D- and L- are a reference to configuration and not to optical behaviour, is more fully dealt with in Chapter X.

---

[1] Scheele, *Kongl. Vetenskaps. Academiens Nya Handlingar.*, 1780, **1**, 116.

[2] Strecker, *Ann.*, 1850, **75**, 27 and 42.

Chemically, there is a great similarity between lactic and glycollic acids. Lactic acid forms anhydrides, several of which are entirely analogous to those from glycollic acid; e.g., when lactic acid is heated for a short time an ester form is obtained (297) which on further heating passes into lactide (298).



(297) (298)

Lactic acid has an important biochemical significance, being not only one of the end-products of a long series of degradations of glycogen which occur during the contraction of muscle-fibre, but being capable of a partial *in vivo* resynthesis to glycogen during recovery periods, after fatigue. Indeed, muscular fatigue has often been described as due to the accumulation of lactic acid in the tissues.

Industrially, lactic acid is one of the cheapest of organic acids, and is widely used in dyeing as a leveller in the bath and as an oxidisable substance for chromate mordanting. It also finds an application as a 'sour' in tanning.

β-Hydroxypropionic acid (often called β-lactic acid or hydracrylic acid) is best prepared by the addition of water to acrylic acid, to which it reverts when

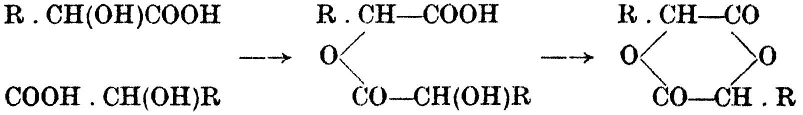
$$CH_2{=}CH\,.\,COOH + H_2O \rightleftharpoons CH_2OH\,.\,CH_2\,.\,COOH$$

treated with dehydrating agents or on heating. Some details of other hydroxy-monobasic acids are given in Table XXXVI. Reference has already been made to the decomposition of α-hydroxy acids to give formic acid and an aldehyde (see Chap.VI, p. 381).

$$R\,.\,(CH_2)_nCH(OH)COOH \longrightarrow R\,.\,(CH_2)_nCHO + HCOOH$$

LACTONES

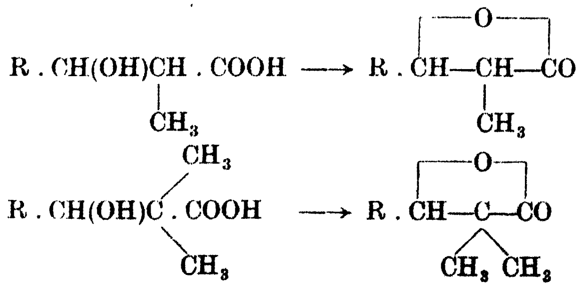
It will have been observed from the material in the preceding section that much of the data available relating to the hydroxy acids is concerned with the formation of anhydrides and lactones. In general, the loss of water from α-hydroxy acids leads to the formation of analogues of lactide, often through an intermediate ester stage which can be isolated :—



β-Hydroxy acids, when unsubstituted, lose water to give unsaturated acids :—

$$R\,.\,CH(OH)CH_2COOH \longrightarrow R\,.\,CH{=}CH\,.\,COOH$$

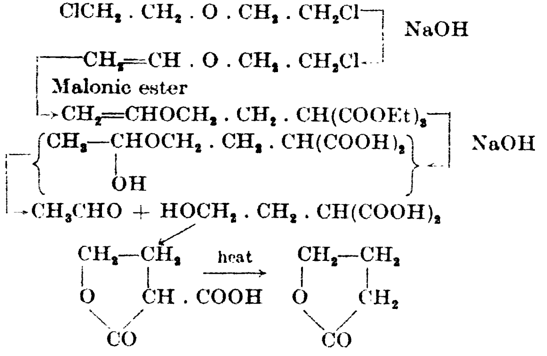
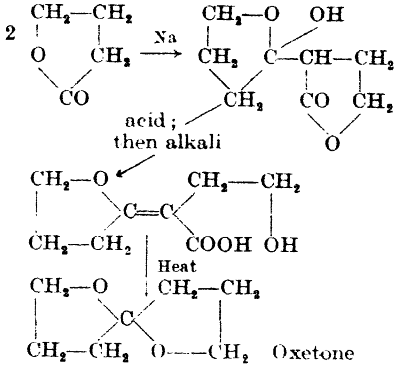
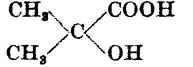
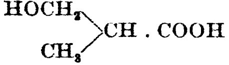
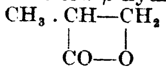
If, however, the α-carbon atom carries one or more alkyl groups a β-lactone is obtained :—



In the latter case, of course, no alternative route is available.

TABLE XXXVI

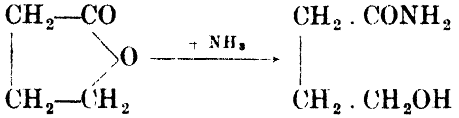
Some Monohydroxy Monobasic Acids

Acid	Mode of preparation	Properties
α-Hydroxybutyric acid **$CH_3CH_2CH(OH)COOH$**	(*a*) From propionaldehyde and HCN; followed by hydrolysis (*b*) From butyric acid *via* α-chlorobutyric acid and hydrolysis	A syrupy liquid; gives a 'lactide' on heating
β-Hydroxybutyric acid **$CH_3 . CH(OH)CH_2 . COOH$**	(*a*) From butyric acid by direct oxidation with H_2O_2 or *via* the β-chloro acid and reduction (*b*) Reduction of acetoacetic ester and hydrolysis	The *d*- and *l*-acids have m.p. 46–48°. $(\alpha)_D \pm 25°$. It appears to be the precursor of acetoacetic acid in the body-fluids of diabetics
γ-Hydroxybutyric acid **$CH_2OH . CH_2 . CH_2 . COOH$**	(*a*) From ethylene chlorhydrin in the malonic ester synthesis (q.v.) (*b*) From dichloro ether:— 	Exists only in solution, since the free acid spontaneously dehydrates to give butyrolactone. Gives:— 
α-Hydroxy*iso*butyric acid 	(*a*) Hydrolysis of acetone cyanhydrin (*b*) By heating acetone and chloroform with alkali (*c*) By direct oxidation of the labile tertiary hydrogen of *iso*-butyric acid	Resembles the corresponding straight-chain compound Very easily oxidised
β-Hydroxy*iso*butyric acid 	(*a*) Owing to its strong tendency to lose water and pass into α-methyl acrylic acid, only the ester can be prepared in good yield, from $(CH_2O)_3$ + Zn and α-bromopropionic ester	One of the few β-hydroxy acids giving a lactone 

The large class of lactones is mainly derived from the γ- and higher hydroxy acids. In the case of γ-hydroxy acids the proximity, stereochemically, of the hydroxyl and carboxyl groups makes it difficult to isolate the free acid, without dehydration ; so that in many cases whilst the lactone of an acid is quite well known, the acid itself is seldom met with ; such an instance is butyrolactone (Table XXXVI) and γ-hydroxybutyric acid. Lactones are often named by the use of the termination ' olide ', e.g., ' 1, 4-butanolide ', for ' butyrolactone '.

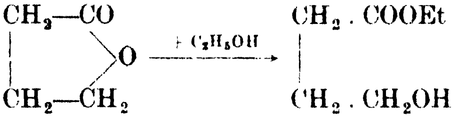
Lactones, of which butyrolactone may be taken as the prototype, are comparatively stable substances, and may be distilled, in some cases, without decomposition. With reagents. the ring is often opened with the regeneration of a derivative of the γ-hydroxy acid, e.g.,

(1)



γ-Hydroxybutyramide

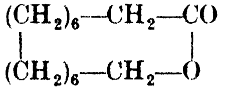
(2)



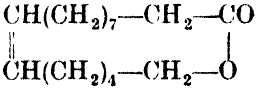
γ-Hydroxybutyric ester

The ' oxetone ' formation indicated in Table XXXVI for butyrolactone is a general reaction, and yields substituted *spiro* compounds of considerable stereochemical interest.

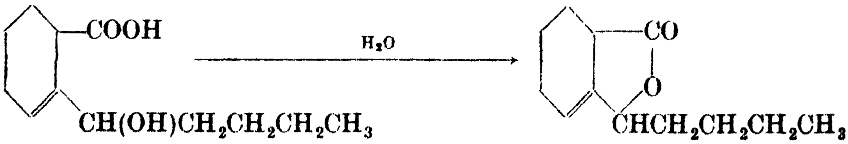
The γ- and ε- hydroxy acids also yield lactones, and some of the higher lactones are of considerable interest on account of their musk-like odour. Thus, the musk-odoriferous principle of angelica root is the so-called ' angelica lactone ' investigated by Kerschbaum [1] and shown to be the lactone of pentadecanol-acid-1 (ω-Hydroxypentadecylic acid) (299). Reference has already been made to this substance in an Appendix to Chapter VI, but it may be added here that it is closely related to the lactone ambrettolide, found in muskseed and extracted for purposes of perfumery (300). Another interesting lactone is sedanolide (302), the substance responsible for celery odour. It is the lactone of sedanonic acid (301) and is a derivative of *cyclo*hexene



(299) Angelica lactone



(300) Ambrettolide



(301)

(302) Sedanolide

The work of Adams has shown that there is a gap in the formation of lactones as the series is ascended and that whilst the lower (γ, δ, ε, etc.), hydroxy acids form lactones there is a group of acids in which 9, 10, and 11 carbon atoms separate the hydroxyl and carboxyl groups. These acids are too large to form the normal ring, and not large enough to form the strainless ring similar to that of angelica lactone. They lose water on heating to form polymers of the type :—

$$HO(CH_2)_9COO[(CH_2)_9COO]_n(CH_2)_9COOH$$

---

[1] Kerschbaum, *Ber.*, 1927, **60**, 902.

TABLE XXXVII

SOME HIGHER HYDROXY ACIDS

Acid	Formula	Preparation	Properties, etc.
9-Hydroxystearic-	$CH_3(CH_2)_8CHOH(CH_2)_7COOH$	From 9-undecanoyl bromide	m. 74–75°
10-Hydroxystearic-	$CH_3(CH_2)_7CHOH(CH_2)_8COOH$	See Adams *et al.*, *J.A.C.S.*, 1927, **49**, 522	m. 81–82°
11-Hydroxystearic-	$CH_3(CH_2)_6CHOH(CH_2)_9COOH$		
12-Hydroxystearic-	$CH_3(CH_2)_5CHOH(CH_2)_{10}COOH$		
12-Hydroxydodecane-	$CH_2OH(CH_2)_{10}COOH$	Occurs naturally; synthesised by Adams[1] from the aldehyde[2, 3]	Sabinic acid, m. 78–79°
16-Hydroxyhexadecane-	$CH_2OH(CH_2)_{14}COOH$	Occurs in leaves of *Pinus* and *Abieta* species.[4] Synthesised by Ruzicka and Stoll.[5]	Juniperinic acid; has powerful musk odour
11-Hydroxyhexadecane-	$CH_3(CH_2)_4CHOH(CH_2)_9COOH$	From 10-aldehydodecane acid methyl ester and $C_5H_{11}MgBr$.[6]	Jalapinolic acid
9, 10-Dihydroxystearic (cis)	$CH_3(CH_2)_7CHOH . CHOH(CH_2)_7COOH$	From acid oxidation of oleic acid	m. 95°
9, 10-Dihydroxystearic (trans)	$CH_3(CH_2)_7CHOH . CHOH(CH_2)_7COOH$	By alkaline oxidation of oleic or elaidic acids	m. 132°
3, 12-Dihydroxypalmitic-	$CH_3(CH_2)_3CHOH(CH_2)_8CHOH . CH_2COOH$	Obtained from rhamnoconvolvalic acid	
9, 10, 16-Trihydroxypalmitic-	$CH_2OH(CH_2)_5CHOH . CHOH(CH_2)_7COOH$	Obtained from shellac. Decomp. with 3 % KOH to azelaic and 7-Hydroxyheptoic acid[7]	
9, 10, 12, 13-Tetrahydroxy-palmitic-	$CH_3(CH_2)_2(CHOH)_2CH_2(CHOH)_2(CH_2)_7COOH$	From wallflower seed oil,[8] human fat[9] and bark,[10] also by oxidising 9, 12-linolenic acid	Sativic acid
16-Hydroxyhexadecene-7-	$CH_2OH(CH_2)_7CH{=}CH(CH_2)_5COOH$	A precursor of ambrettolide, found in musk-seed	Ambrettolic acid
12-Hydroxyoctadecene-9-	$CH_3(CH_2)_5CHOH . CH_2 . CH{=}CH(CH_2)_7COOH$	In the form of its glyceride is the main constituent of castor oil (see text)	m. 5° Ricinoleic acid (12-Hydroxyoleic acid)

---

[1] Adams, *J.A.C.S.*, 1929, **51**, 625.

[2] Simonsen *et al.*, *J.C.S.* **1928**, 2678.

[3] P. Chuit and J. Hausser, *H. Ch. Acta*, 1929, **12**, 463.

[4] Bougault and Chattelain, *C.R.*, 1928, **186**, 1746.
Ruzicka and Stoll, *H. Ch. Acta*, 1928, **11**, 1159.

[6] Davies and Adams, *J.A.C.S.*, 1928, **50**, 1749.

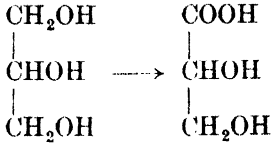
[7] Nagel and Mertens, *Ber.*, 1936, **69B**, 2050.

[8] van Loon, *Rec. Trav. Chim.*, 1930, **47**, 745.

[9] O. Wagner, *Biochem. Z.*, 1926, **174**, 412.

[10] Zellner, *Monats.*, 1926, **46**, 611.

Glyceric acid is the simplest dihydroxy monocarboxylic acid, and is usually obtained by the controlled oxidation of glycerol, a method discovered by Debus [1] and Sokolov.[2] They used nitric acid and by placing a layer of dilute nitric acid over one of glycerol in a tall cylinder allowed the diffusion of the heavier layer into the lighter to control the rate of oxidation. The substance so



$$\begin{array}{c} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

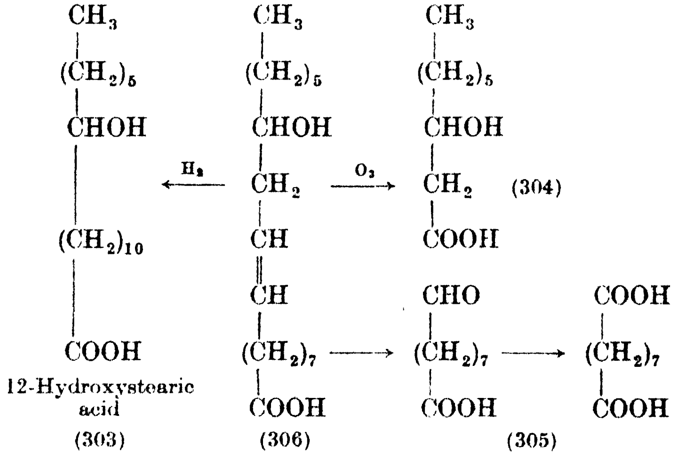
prepared is a thick syrup, which is optically inactive, although it has been resolved into *dextro-* and *lævo*-rotatory forms, but these readily racemise on standing in aqueous solution.

The higher polyhydroxy acids are so intimately related to sugar chemistry that their consideration is deferred to Chapter X. Of the many higher acids containing one or more hydroxyl groups, Table XXXVII gives examples which serve to illustrate the general properties of the group.

In the table are included some unsaturated long-chain hydroxy acids, of which ricinoleic acid is of particular importance. There is ample evidence for the structure of ricinoleic acid (306).

(1) It yields 12-hydroxy stearic acid on hydrogenation (303).
(2) On ozonolysis it yields 3-hydroxypelargonic acid (304)

together with the half aldehyde of azelaic acid and azelaic acid (305) itself.



$$\begin{array}{c} CH_3 \\ | \\ (CH_2)_5 \\ | \\ CHOH \\ | \\ (CH_2)_{10} \\ | \\ COOH \end{array} \xleftarrow{H_2} \begin{array}{c} CH_3 \\ | \\ (CH_2)_5 \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ CH \\ \| \\ CH \\ | \\ (CH_2)_7 \\ | \\ COOH \end{array} \xrightarrow{O_3} \begin{array}{c} CH_3 \\ | \\ (CH_2)_5 \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOH \\ \\ CHO \\ | \\ (CH_2)_7 \\ | \\ COOH \end{array} \begin{array}{c} (304) \\ \\ \\ \\ \longrightarrow \end{array} \begin{array}{c} COOH \\ | \\ (CH_2)_7 \\ | \\ COOH \end{array}$$

12-Hydroxystearic acid (303) (306) (305)

There is also a most ingenious application of the Beckmann rearrangement to the study of the structure of ricinoleic acid. The acid (307) was converted to its dibromo addition compound, and thence *via* the acetylene to the ketone, which gave an oxime (308). This evidently consisted of both possible forms since on Beckmann rearrangement it gave two amides (309 and 310) which on hydrolysis yielded the four substances :—

(1) 2-Hexyltrimethylene imine (311).
(2) Azelaic acid (312).
(3) 4-Hydroxycapric acid (313).
(4) 8-Aminocaprylic acid (314).

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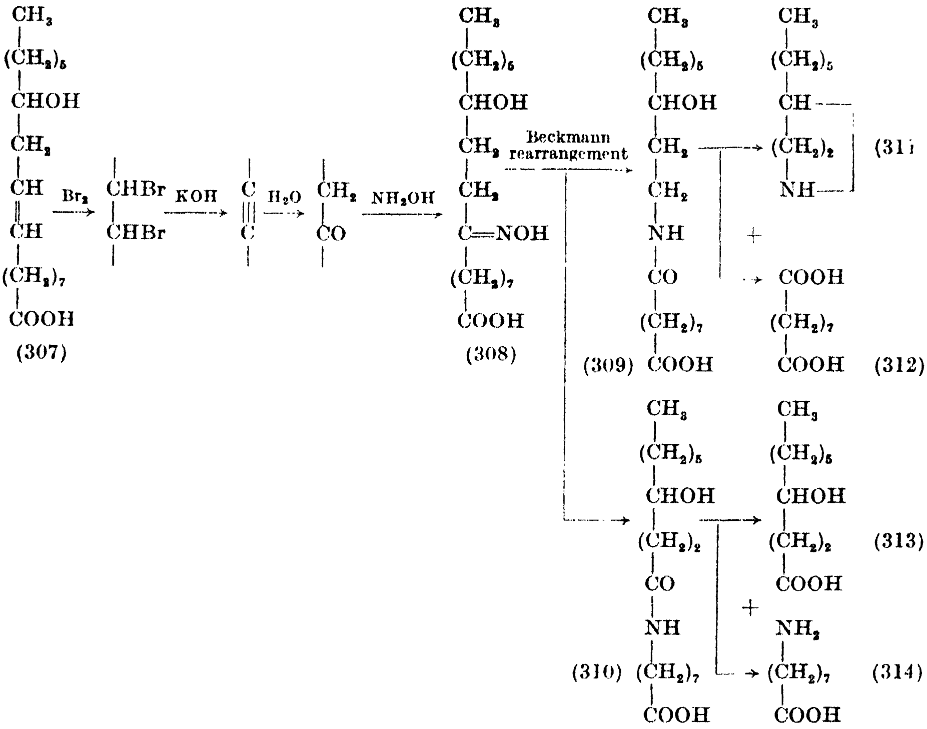
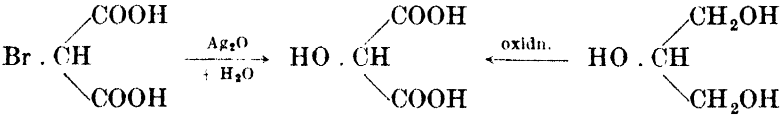
[1] Debus, *Ann.*, 1858, **106**, 79 ; 1859, **109**, 227.
[2] Sokolov, *ibid.*, 1858, **106**, 95.



(307) (308) (309) (310) (311) (312) (313) (314)

THE HYDROXY DIBASIC ACIDS

The simplest hydroxy dibasic acid is tartronic acid (315), produced by the reaction of bromomalonic acid with a suspension of silver oxide, or by the



$$Br.CH(COOH)_2 \xrightarrow[+H_2O]{Ag_2O} HO.CH(COOH)_2 \xleftarrow{\text{oxidn.}} HO.CH(CH_2OH)_2$$

(315)

oxidation of glycerol with cold dilute permanganate. The acid is difficult to obtain in quantity, but crystallises well from water in large prisms, which melt about 180° with evolution of carbon dioxide. It is mainly of interest in relation to its ureide—dialuric acid (Chap. VI, Vol. II).

Malic acid is the best known of the mono-hydroxy acids of this series; Monro[1] showed that the juice of apples contains an acid which neutralised soda, but it was Scheele[2] in 1785, who showed that it was distinct from citric acid, and named it 'malic' acid. The acid is of exceedingly wide distribution in fruits and vegetable structures and in Table XXXVIII is shown some of the forms of its occurrence. Historically, our knowledge of malic acid has followed a path very similar to that of lactic acid; the individuality of both acids was demonstrated by Scheele, and both acids were subsequently held by Bouillon-Lagrange and Vögel to be merely impure acetic acid; whilst the nature of both was conclusively settled by Liebig. The most economical natural source of malic acid is the acid calcium malate which separates from maple syrup and is filtered off before bottling. This can be recrystallised and decomposed with dilute sulphuric acid to give a solution of malic acid which when evaporated in the water-bath gives a syrup that crystallises on cooling, and after inoculation with a crystal of the solid acid.

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[1] Monro, *Phil. Trans.*, 1767, p. 479.

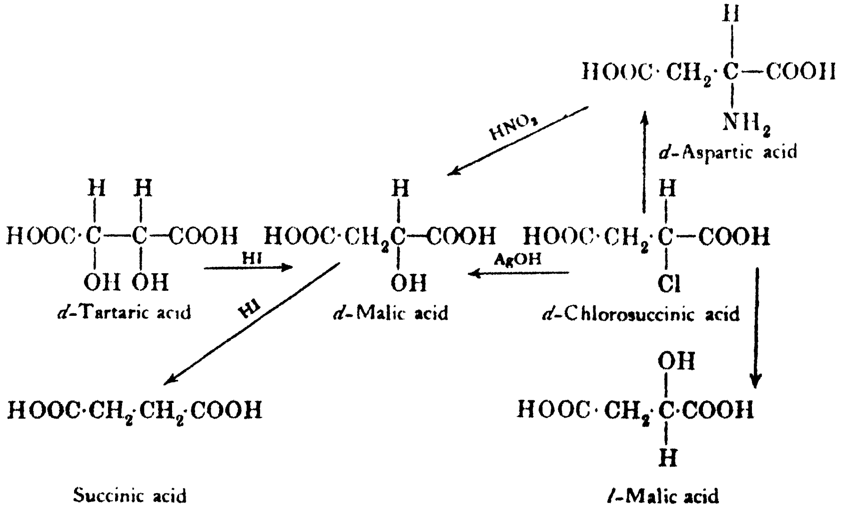
[2] Scheele, *Longl. Vetenskaps. Acadamie-Nya. Handlingar*, 1785, **6**, 17.

TABLE XXXVIII

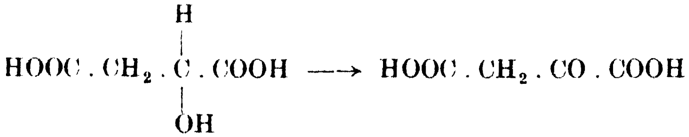
OCCURRENCE OF MALIC ACID AND ITS SALTS

Source	Form
Apples, pears, gooseberries	Free malic acid
Mountain Ash berries, *Berberis*	
Leaves and vegetable parts of *Begonia*, *Mesembryanthemum*, *Cactaceæ* and *Crassulaceæ*	
Quince, red and white currants	
Raspberries, blackberries, pineapple	
Cherries (Morello)	
Sweet cherries, leaves and stems of rhubarb	Acid potassium malate
Maple sap	Acid calcium malate
Leaves of house-leek (*Sempervivum tectorum*), leaf of *Nicotinia* species, and berries of the sumach species, especially *Rhus coriaria*	

The malic acid of natural origin is *lævo*-rotatory in dilute solutions but its optical activity is anomalous, for at a concentration of 34 per cent. (in water) the solution is optically inactive and further additions of acid render the solution *dextro*-rotatory. The optical isomer—the so-called *d*-malic acid is best obtained by the reduction of *d*-tartaric acid, with hydriodic acid of density 1·6. It can also be obtained by the action of nitric acid on *d*-aspartic acid, or by taking advantage of the Walden inversion from *l*-malic acid, which is converted by phosphorus pentachloride to *d*-chlorosuccinic acid, and the latter into *d*-malic acid by a suspension of silver oxide. These changes are shown in the diagram below :—



It is also possible to obtain racemic malic acid by heating maleic anhydride with water under pressure, in the presence of a little alkali, which should make the acid a cheap commodity. The sodium salt tastes like sodium chloride, and is used dietetically where a low 'salt' diet is required. Chemically, malic acid presents few points of interest; it is oxidised to oxalacetic acid under suitable conditions :—



$$HOOC.CH_2.\overset{H}{\underset{OH}{C}}.COOH \longrightarrow HOOC.CH_2.CO.COOH$$

Tartaric Acid.—The deposition of 'tartar' or 'argol' on the interiors of wine barrels during the process of maturing has been known since the earliest times, and the deposit when dried has been esteemed as a metallurgical flux and as a source of alkali upon ignition. Many thought the substance to be an acid and in early Pharmacopœias, the purified 'cream of tartar' was described as 'acidum tartari'. Scheele first isolated true tartaric acid in 1769, but owing to the dilatory action of Bergmann, to whom the discovery was communicated, no account was published until the following year. Shortly afterwards tartaric acid was manufactured in considerable quantity.

Fresh attention was directed to the subject when, in 1819, John, of Berlin described an acid which was being manufactured in the Vosges, and which appeared to be a new substance, much like tartaric acid but differing from it in certain particulars. Gay-Lussac, in 1825, obtained from Kestner, the manufacturer in Thann, a quantity of the new acid, which had been prepared as a by-product in Kestner's factory, during the manufacture of tartaric acid. Kestner also noticed that this acid (afterwards termed 'racemic' acid) only appeared when the solutions were boiled considerably, and disappeared entirely when the liquors were evaporated in vacuum at 50° (one of the earliest applications of the famous 'Kestner' evaporator).

Pasteur's attention was directed to these acids in 1853, when he showed that tartaric acid could be converted into racemic acid. It was in studying the reverse procedure that he crystallised sodium ammonium racemate and observed that two kinds of crystals were obtained, identical save for the position of the hemihedral facets which in some occurred on the right-hand side and in others upon the left, as in the figure below :—

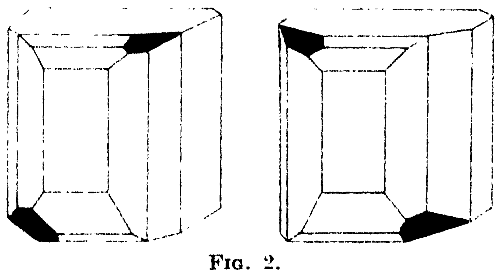


FIG. 2.

A. Dextrorotatory Sodium Ammonium tartrate.
B. Lævorotatory Sodium Ammonium tartrate.
[Hemihedral facets black.]

He sorted the two types and showed that those crystals which are *dextro*-hemihedric are *dextro*-rotatory in solution, whilst their mirror image types give a *laevo*-rotatory solution. In this way racemic acid could be separated into *d*- and *l*-forms, and the foundations were laid of the study of optical isomers.

That racemic acid is a definite compound has been shown by a variety of means; Pasteur showed that when concentrated solutions of *d*- and *l*-tartaric acid were mixed, at such concentrations that there was no tendency for the solid acids to separate, heat is evolved and the racemic acid crystallises, being only about one-sixth as soluble as the active forms.

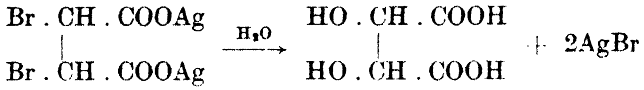
The second inactive or mesotartaric acid was obtained by Pasteur by heating cinchonine-*d*-tartrate to 170°. It is most easily obtained by autoclaving a mixture of six parts of tartaric acid and one of water at 165°. It is also formed by the permanganate oxidation of maleic acid.

There is little difference between the *d*- and *l*- acids in general physical properties (apart from their optical activity), but the racemic and mesotartaric acids differ from each other and from the active forms in most respects ; thus :—

	Racemic-	*d*- and *l*-	Meso-
	Tartaric acids		
K	$9{\cdot}7 \times 10^{-4}$	$9{\cdot}7 \times 10^{-4}$	6×10^{-4}
M.p.	206°	170°	140°
Water of crystallisation	Monohydrate	Anhydrous	Monohydrate
Solubility in water at 10°	21	137	20
Solubility in alcohol at 10°	2	37	167

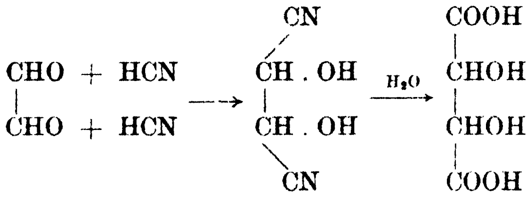
d-Tartaric acid and its salts are valuable industrial and medicinal chemicals. The acid is used as a dyebath assistant and as a partial replacement of citric acid in lemonade powders, and as the basis of some effervescent salines ; cream of tartar is used as a component of baking powder and Rochelle salt, the sodium potassium, *d*-tartrate tetrahydrate, is used in Seidlitz powders, and in the preparation of Fehling's solution.

Tartaric acid has been obtained by boiling the silver salt of dibromosuccinic acid with water, when the reaction



$$\begin{array}{l} \text{Br . CH . COOAg} \\ \quad | \\ \text{Br . CH . COOAg} \end{array} \xrightarrow{H_2O} \begin{array}{l} \text{HO . CH . COOH} \\ \quad | \\ \text{HO . CH . COOH} \end{array} + 2AgBr$$

takes place.[1] Glyoxal dicyanhydrin gives the meso acid, with some racemic acid on hydrolysis :—



$$\begin{array}{l} \text{CHO + HCN} \\ | \\ \text{CHO + HCN} \end{array} \longrightarrow \begin{array}{l} \quad\text{CN} \\ \;/ \\ \text{CH . OH} \\ | \\ \text{CH . OH} \\ \;\backslash \\ \quad\text{CN} \end{array} \xrightarrow{H_2O} \begin{array}{l} \text{COOH} \\ | \\ \text{CHOH} \\ | \\ \text{CHOH} \\ | \\ \text{COOH} \end{array}$$

So far, no method of chemical manufacture has been devised to displace the natural acid, which is widely spread, occurring in potatoes, cucumbers, caragheen moss, pepper, the celandine and many other plants, albeit in small quantity. Higher analogues of tartaric acid, such as phloionic acid,

$$HOOC(CH_2)_7CHOH \,.\, CHOH \,.\, (CH_2)_7COOH$$

are found in cork.

Citric Acid.—Once again it is Scheele to whom we owe the first separation of citric acid from lemon juice. In his monograph entitled 'Observations on Lemon Juice and on the method of crystallising it ',[2] he describes a process for the preparation of citric acid which is substantially that now used for the recovery of citric acid from lemon juice and the pineapple waste of the canneries.

Considerable amounts of citric acid are made by the fermentation process in which glucose is subjected to the action of *Citromyces*, a mould capable of converting about 50 per cent. by weight of the carbohydrate to citric acid, which may be then worked up by the calcium process.

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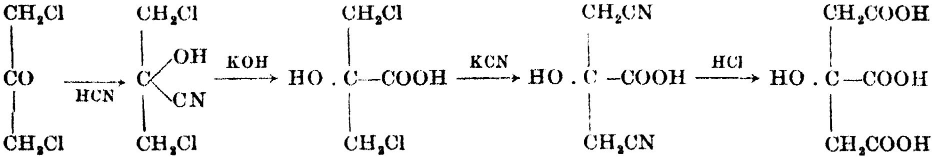
[1] Kekule, *Ann.*, 1858, **107**, 124.

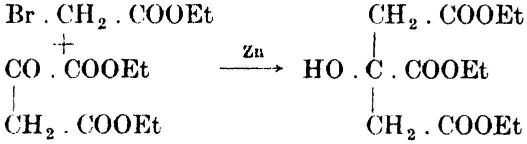
[2] Scheele, *Kongl. Vetenskaps. Academie Nya Handlingar*, 1784, **5**, 105.

No satisfactory industrial synthesis of citric acid has been achieved, but it can be made by a variety of processes for the purpose of establishing the constitution. Thus, dichloroacetone with HCN gives the cyanhydrin (316) which gives the dichlorohydroxy acid (317) on hydrolysis. This on reaction with alkali cyanide yields the dinitrile (318) which can be hydrolysed to citric acid (319).



(316) (317) (318) (319) Citric acid

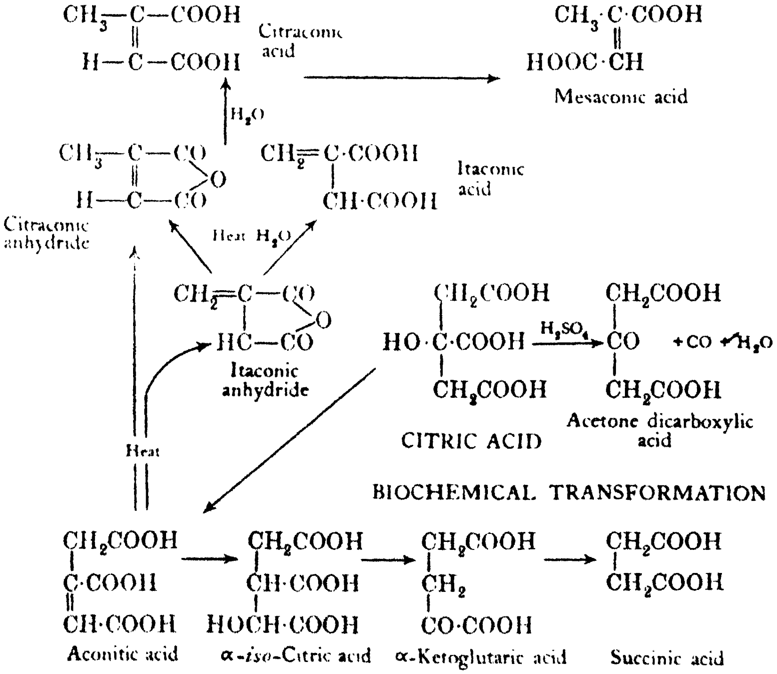
Alternatively, the triethyl ester of citric acid may be obtained by carrying out Reformatzski's reaction with α-bromoacetic ester, oxaloacetic ester, and zinc[1] (320). Only about 6 per cent. of citric ester (321) is obtained, but this is sufficient to indicate the correctness of the accepted formula for its structure.



(320) (321)

The decompositions of citric acid are important, and although in some cases they have been previously mentioned, the course of the main reactions is brought together in the following diagram :—

THE DECOMPOSITIONS OF CITRIC ACID



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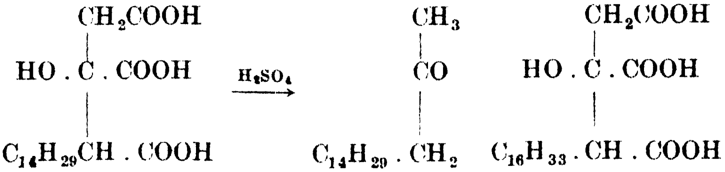
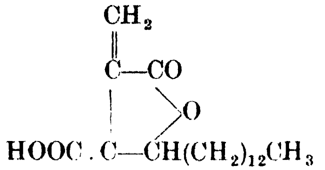
[1] Lawrence, *J.C.S.*, 1897, 71, 457.

A number of α-substituted alkyl citric acids are found in various plant sources. Thus, caperatic acid, the methyl ester of *nor*-caperatic acid is found in *Parmetia caperata*, a Japanese plant.[1] *nor*-Caperatic acid is α-tetradecylcitric acid (322).



$$\underset{(322)}{\mathrm{HO\cdot \overset{CH_2COOH}{\underset{C_{14}H_{29}CH\cdot COOH}{C}}\cdot COOH}} \xrightarrow{H_2SO_4} \underset{(323)}{\mathrm{\overset{CH_3}{\underset{C_{14}H_{29}\cdot CH_2}{CO}}}} \qquad \underset{(324)}{\mathrm{HO\cdot \overset{CH_2COOH}{\underset{C_{16}H_{33}\cdot CH\cdot COOH}{C}}\cdot COOH}}$$

(322) (323) (324)

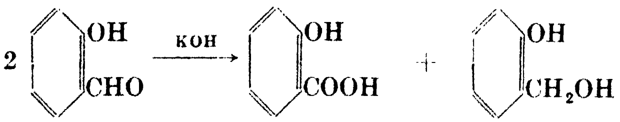


(325)

The action of concentrated sulphuric acid on tetradecylcitric acid is to convert it to methyl pentadecylketone (heptadecanone-2) (323). The analogous cetyl citric acid is agaracinic acid [2] (324) and has been synthesised from cetyl iodide and the mono-sodio derivative of acetone dicarboxylic ester. The cetyl-keto body is then treated with phenyl carbimide in acetic acid and the intermediate product hydrolysed. Protolichesteric acid (325) [3] is a derivative of tetradecylitaconic acid, being formed by ring formation between the OH of the central carboxyl group and the first carbon of the alkyl chain. Many similar acids exist, but their biological significance remains undiscovered.

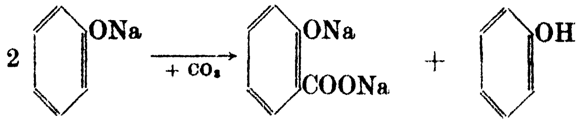
Aromatic Hydroxy Acids

The simplest hydroxy acids of the aromatic series are *o*-, *m*- and *p*-hydroxybenzoic acids. The first, salicylic acid, was discovered by Piria in 1838; he obtained it by heating salicylaldehyde with aqueous potash, a reaction resembling the Cannizzaro method,[4] presumably



It was also observed when salicin (the glycoside from willow-bark) is fused with potash, or when the methyl ester contained in oil of wintergreen (*Gaultheria procumbens*) is saponified.

The manufacture of salicylic acid is carried out by Schmitt's modification of Kolbe's process. In the original method of Kolbe, carbon dioxide was passed into sodium phenate at 180–200° whereby the reaction



took place; not only was the best possible yield of salicyclic acid only 50 per cent., but the separation from phenol had to be undertaken. Schmitt showed that when a lower temperature was used for the absorption of carbon dioxide an intermediate phenyl carbonate was obtained which at 120–145° passed almost quantitatively into sodium salicylate :—

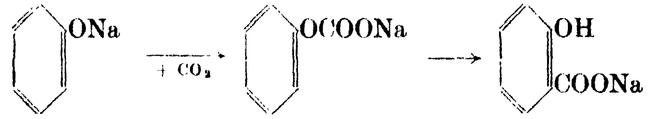
---

[1] Asano and Ohta, *Ber.*, 1933, **66B**, 1020.

[2] Passerini and Banti, *Atti. III, Cong. naz. chim. pur. applicata*, 1930, 343.

[3] Asano and Kanematsu, *Ber.*, 1932, **65B**, 1175.

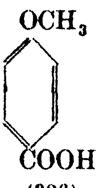
[4] Piria, *Ann. Chim. Phys.*, 1838, **69**, 298; *Ann.*, 1839, **30**, 165.



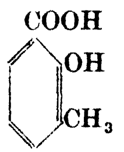
Salicylic acid can be purified by distillation in a current of superheated steam. It forms colourless needles, m. 158·5° ; it is only slightly (2 gm./per litre at 20°) soluble in cold water ; but is more soluble in boiling water (75 gm./litre). The acyl alkyl derivatives of salicylic acid are widely used in medicine, mainly on account of the antipyretic and analgesic action of the salicyl group. Acetyl salicylic acid (aspirin) is one of the most widely used medicinal chemicals and is prepared from acetic anhydride and salicylic acid in acetic acid, using a small quantity of sulphuric acid as catalyst. Methyl salicylate is used widely in treating rheumatic conditions and salol, phenyl salicylate, is used as an intestinal antiseptic, for whereas simple salicylates are hydrolysed and absorbed in the stomach the phenyl ester passes unchanged through that organ, and is only hydrolysed in the lower portion of the tract. *m*-Hydroxybenzoic acid, m. 201°, was first obtained by Gerland [1] by the action of nitrous acid on *m*-aminobenzoic acid. It may be more conveniently prepared by the fusion of benzoic-*m*-sulphonic acid with caustic potash. It offers no outstanding points of chemical interest, and is used industrially in small quantities for certain azo dyes.

p-Hydroxybenzoic acid, m. 213°. This acid is produced in considerable quantity if the temperature in the industrial salicylic acid synthesis is raised to 200°. If potassium hydroxide is used in place of caustic soda and the temperature is maintained at 190–200°, the yield of *p*-hydroxy acid is almost quantitative. Some *p*-hydroxy benzoic acid can be obtained from the Reimer-Tiemann reaction between aqueous sodium phenate and carbon tetrachloride. Anisic acid is the methyl ether of *p*-hydroxybenzoic acid (326).

Of the cresotinic acids, only the vicinal *o*-hydroxy-*m*-methylbenzoic acid (327) is of any importance, being obtained by Kolbe's method from *o*-cresol ; some *p*-hydroxy-*m*-methylbenzoic acid (328) is formed during the process.



(326)



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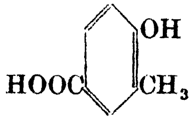
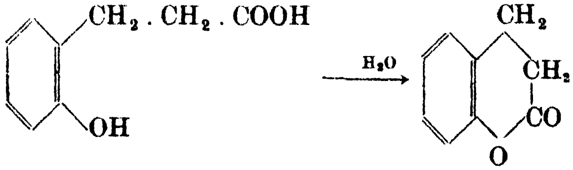


(328)

Melilotic and phloretic acids, *o*- and *p*-hydroxy phenylpropionic acids are two homologues of salicylic acid which are of natural occurrence ; melilotic acid, m. 83°, (329) which occurs in *Melilotus officinalis* [2] is a white crystalline substance which readily passes over into the lactone (330). Its unsaturated



(329) (330)

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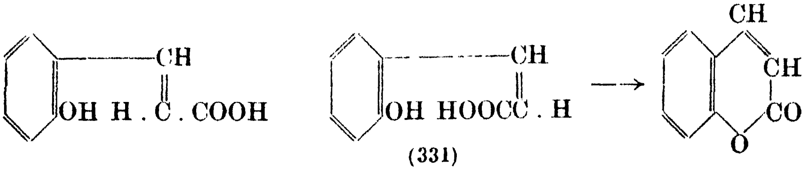
[1] Gerland, *Ann.*, 1853, **86**, 143 ; 1854, **91**, 189.

[2] Bodenbender, *ibid.*, 1863, **126**, 262.

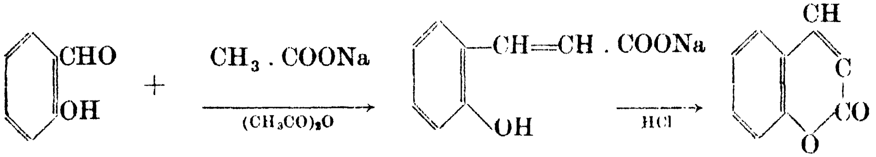
analogue, *o*-hydroxycinnamic acid, exists in the usual *cis*- and *trans*- modifications. The *trans*-modification, m. 208° (331), is obtained by gently warming



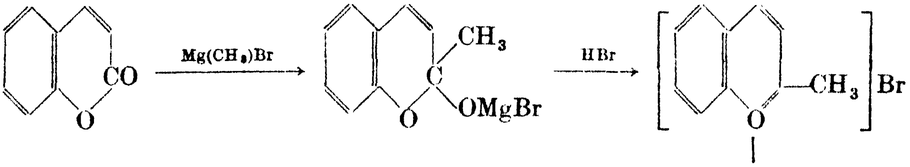
(331)

an aqueous solution of the diazonium compound from *o*-aminocinnamic acid. It shows no tendency to ring formation. The *cis*-acid is only known in the form of its salts, and when liberated passes over immediately into coumarin, a beautifully crystalline substance, m. 67°, b. 290°, with a pleasant odour, characteristic of new mown hay, woodruff—*Asperula odorata*, or Tonquin beans. The latter were once a substantial article of commerce used for scenting snuff.

Considerable quantities of coumarin are made artificially by Perkin's reaction, starting with salicylaldehyde, sodium acetate and acetic anhydride :—

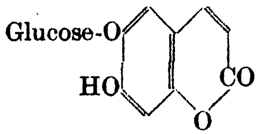


Coumarin affords a valuable link between the aromatic series and the pyrones ; treated with methylmagnesium bromide it gives a Grignard addition compound at the CO group (331*a*). This compound, treated with hydrobromic acid,

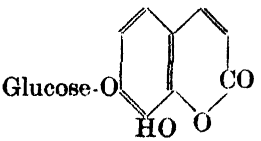


(331*a*) (332)

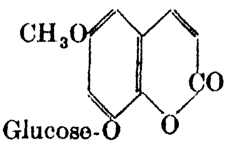
yields a methylbenzpyrylium bromide (332). Coumarin occurs naturally as a simple glycoside, and is frequently accompanied by other glycosides from hydroxycoumarins. Thus, aesculin (from horse chestnuts) is the 6-glucoside of 6, 7-dihydroxycoumarin (333) and daphnin (from *Daphne* species, including *D. Mezereon*) is the 7-glucoside of 7, 8-dihydroxycoumarin (334) ; fraxin (335) is a 6-methoxy derivative.



(333) Aesculin

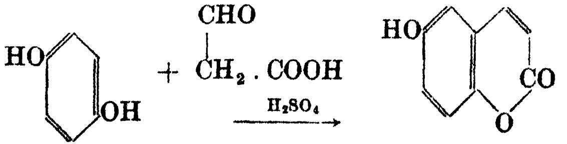


(324) Daphnin



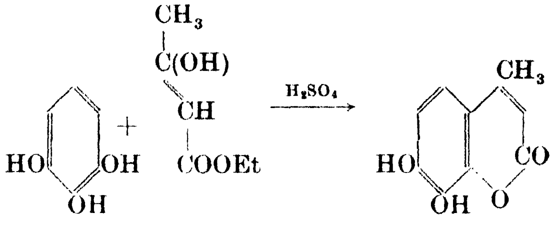
(335) Fraxin

Compounds of this series can be prepared by an extension of Pechmann's synthesis of coumarin, i.e., by the condensation of a polyhydric phenol with malic and sulphuric acids. It has been suggested that the half aldehyde of malonic acid is the active agent in this synthesis :—



6-Hydroxycoumarin

For the 7, 8-dihydroxy coumarin derivatives carrying an alkyl group in the '4' position, the v. Pechmann-Duisberg synthesis is to be preferred. In this method, pyrogallol (or any suitable polyhydric phenol) is condensed with acetoacetic ester in the presence of concentrated sulphuric acid. In the case quoted, 4-methyl-7, 8-dihydroxycoumarin (336) is obtained :—



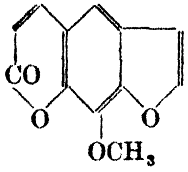
(336)

It may be added that *umbelliferone*, 7-hydroxycoumarin, may be obtained by the former method from resorcinol. It is a crystalline substance, m. 240°, with a persistent fluorescence in ultra-violet light. It occurs naturally in *Daphne mezereon*, and in many members of the *Umbelliferæ*, from which it takes its name. Among the various coumarin aglycones which have been made by these methods, and which occur naturally, the following may be mentioned :—

TABLE XXXIX

Glycoside	Aglycone	M.P.	Source
Fraxetin	6-Methoxy-7, 8-dihydroxycoumarin	227-228°	Types of ash (*Fraxinus*)
Limettin	5, 7-Dimethoxycoumarin	147°	Citrous fruits
Daphnetin	7, 8-Dihydroxycoumarin	256°	*Daphne* species
Bergapten	5-Methoxy-6, 7-furo-coumarin	—	*Citrus bergamina*
Xanthotoxin	8-Methoxy-6, 7-furo-coumarin	—	*Fagara xanthoxyloides*
Angelicin	7, 8-Furo-coumarin	—	Angelica root oil
Imperatorin	8-*Iso*amylenoxy-6, 7-furo-coumarin	—	*Imperatoria ostruthium*
Pimpinellin	5, 6-Dimethoxy-8, 7-furo-coumarin	—	*Pimpinella saxifraga*
Ayapin	6. 7-Methylenedioxycoumarin	—	*Eupatorium ayapana*
Fraxinol	5, 7-Dimethoxy-6-hydroxycoumarin	—	Ash
Osthol	7-Methoxy-8-*iso*-amylidone coumarin	—	Angelica
Osthenol	7-Hydroxy-8-*iso*-amylidone coumarin	—	Angelica

The characteristic structure of the latter group of compounds is shown by the structure of xanthotoxin (337), from which it will be seen that the substances



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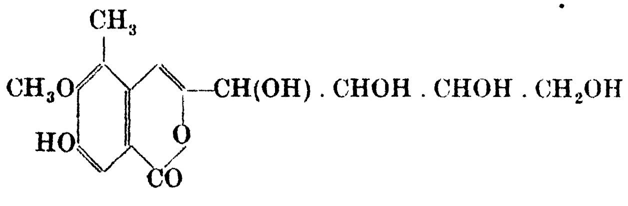
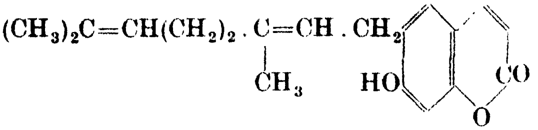


(338)

are coumarin-coumarone derivatives ; the false terminology 'furo-coumarin' is only used in the table above to bring out the resemblance to the simpler members of the series. Many of the substances of this group are strong fish-poisons, and are used by the natives for this purpose. A few *iso*-coumarin members of the group are known of which bergenin (338) from saxifrage roots is the most well-known.

The structures of ostruthin and ammoresinol,[1] from *Imperator ostruthium* and *Doremia ammoniacum* respectively, are shown in (339) and (340) from which it will be observed that they are also members of this series :—



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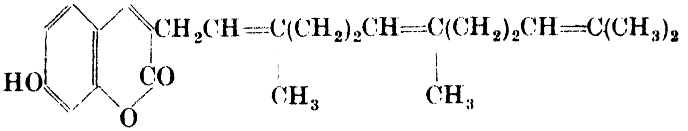
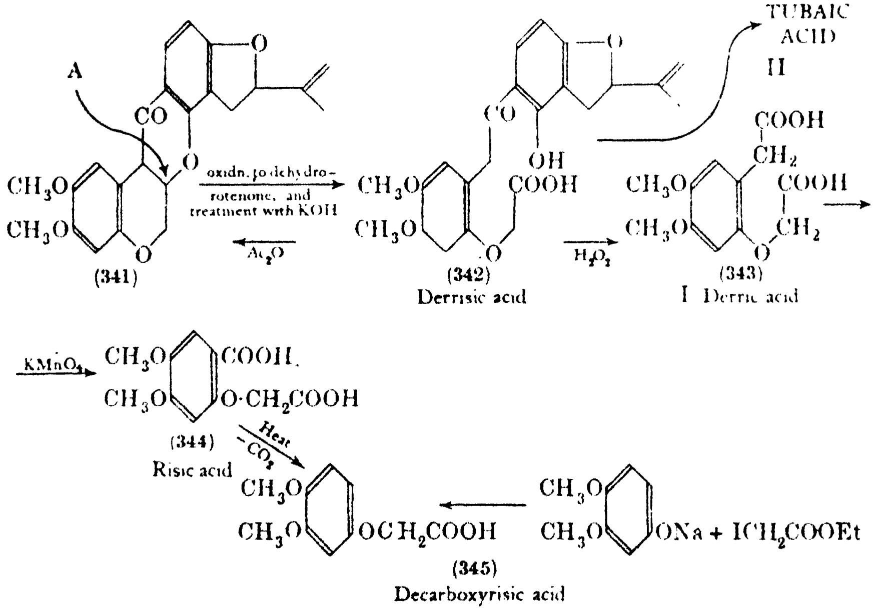


(340)

The poisonous substances of derris are closely related to this series of compounds, and are conveniently considered at this point. Derris and similar roots have for a long time been used as fish poisons, the fish being killed by a very high dilution of material which is quite harmless when consumed by humans. Dilutions up to 1 in 5,000,000 kill goldfish in two hours. The fact that the powder or extract can be used for the extermination of plant pests has made derris preparations of great value, and has led to a close examination of their active constituents. Rotenone, the principal active constituent, has an empirical formula, $C_{23}H_{22}O_6$. It readily parts with two hydrogen atoms (at A in (341)) and the dehydrorotenone so obtained is ' hydrated ' by caustic alkalies, to derrisic acid (342). The action is reversible and dehydrorotenone is regenerated when derrisic acid is warmed with acetic anhydride. Treatment of derrisic acid with hydrogen peroxide leads to a breakdown into two portions, I, derric acid (343) and II, tubaic acid (346). Derric acid loses a methylene group on permanganate oxidation, to form a second dicarboxylic acid, risic acid (344),



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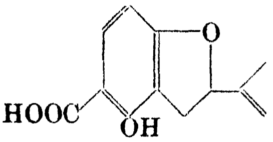
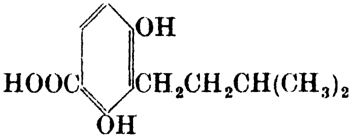
[1] Kunz, Weidle and K. Fischer, *J. Pr. Chem.*, 1934, **141**, 350.

and this may be decarboxylated by heating to give decarboxyrisic acid (345). The constitution of this acid was checked by the synthesis of LaForge,[1] who obtained its ester by the condensation of the sodium derivative of 3, 4-dimethoxyphenol with iodo-acetic ester. The ester was easily hydrolysed to decarboxyrisic acid, identical with that from rotenone.

The structure of tubaic acid was less easily elucidated ; examination showed it to be aromatic ; to contain a carboxyl group, a hydroxyl group which was so placed sterically as not to respond to methylation, and an indifferent ether oxygen. It readily took up two atoms of hydrogen to give a dihydrotubaic acid which, save for absence of unsaturation, appeared almost identical in chemical properties with tubaic acid itself ; from which it is deduced that the unsaturation is in the side-chain. Dihydrotubaic acid can be converted by further reduction to tetrahydrotubaic acid (347), which is, however, a dihydroxy compound, one ether link being broken. Tetrahydrotubaic acid is decarboxylated on heating to 2-*iso*-amyl resorcinol (348). The structure of this substance can readily be determined, and the fact that in tetrahydrotubaic acid one hydroxyl group is indifferent to methylation shows that the carboxyl group must be adjacent, whilst the fact that this indifference persists in tubaic acid itself, shows that the other hydroxyl group must have been formed during the conversion of the dihydro- to the tetrahydro- acid. In this way the structure of tubaic acid and rotenone has been arrived at with a fair degree of certainty.



(346) Tubaic acid



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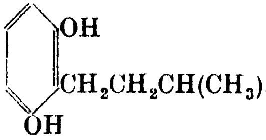
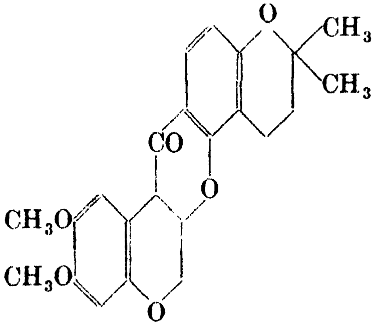
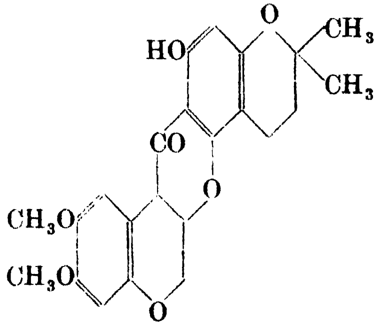


(348)

The fact that extracts of various plants, free from rotenone, were able to exert a strong poisonous effect on fish, led American workers to recognition of other members of this group. Derris was shown to contain toxicarol, tephrosin and deguelin, and *cube* to contain toxicarol and deguelin. These substances proved to have structures similar to those of rotenone ; two are shown below :—



Deguelin



Toxicarol

Phloretic acid is a constituent of the molecule of the glycoside phloridzin. The latter was discovered just over a century ago by Koningk [2] in the root bark of pear, plum and apple trees. The washed bark is shredded and extracted with warm dilute alcohol from which the phloridzin crystallised. It forms needles, m. 108°, at which temperature it loses its two molecules of water of crystallisation, resolidifying and melting at 170–171°. On mild acid hydrolysis, phloridzin (340) yields the aglycone, phloretin (350); alkaline hydrolysis removes phloretic acid (351) forming phlorin (352), the glycoside of phloroglucinol (353). In turn, phloretin may be split down to phloretic acid and phloroglucinol, and phlorin to glucose and phloroglucinol. Phloretic acid, m. 128°, is found also in urine, where it is a product of the metabolism of tyrosine. It was synthesised by Hlasiwetz[1] by the reduction of *p*-hydroxycinnamic acid with sodium amalgam, but is most easily obtained from tyrosine. If 20 litres of a 1 per cent. suspension of finely ground tyrosine is incubated with a few shreds of putrid pancreas for two days, the bulk of the amino-acid is changed to phloretic acid. The filtered liquid is evaporated to a small bulk and extracted with ether. The phloretic acid forms prismatic crystals.

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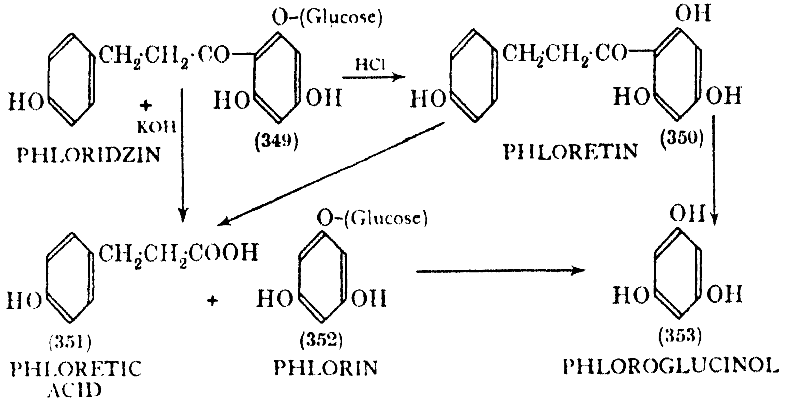
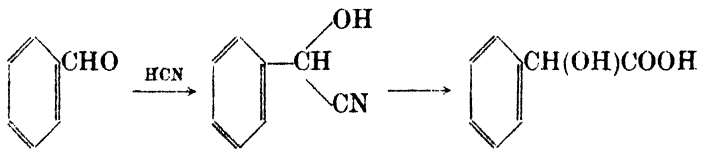
[1] LaForge, *J.A.C.S.*, 1931, **53**, 3896.

[2] Koningk, *Ann.*, 1839, **15**, 75 and 258.



An important group of acids belonging to this series have the hydroxyl group in the aliphatic side-chain. The principal members of the series are mandelic and tropic acids. The natural occurrence of mandelic acid derivatives as glycosides is fully discussed in Chapter X, and need not be again referred to; the synthesis was first effected as long ago as 1836 by Winckler[2] from benzaldehyde, hydrocyanic and hydrochloric acids. The method is still used for its production, an emulsion of benzaldehyde in sodium cyanide solution being treated with hydrochloric acid and the nitrile so obtained, hydrolysed by heating at 100° in the liquid in which it has been prepared. The acid forms plates with a characteristic smell and unpleasant taste. The racemic form melts at 119° and the active forms at 134°. The use of mandelic acid and its ammonium salt in medicine, depends on its excretion unchanged in the urine, which, if made acid by the administration of suitable buffer salts, becomes bacteriostatic.



Acids of the mandelic series are easily prepared by the various modifications of Reformatzki's reaction. Thus, if tetralone be subjected to the action of zinc and bromoacetic ester, a hydroxy ester is obtained which readily loses water.

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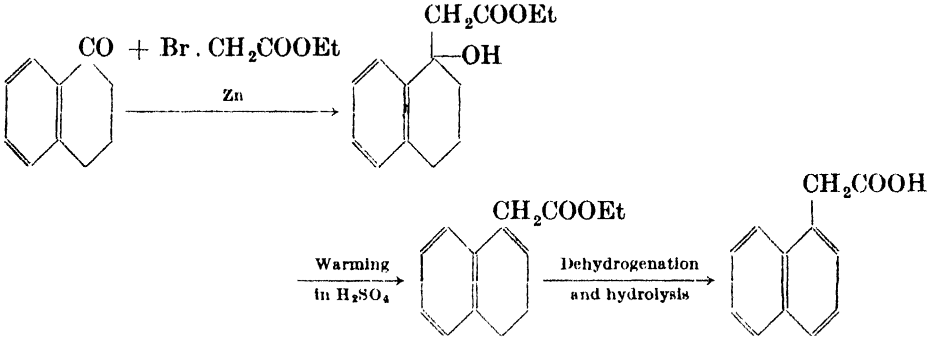
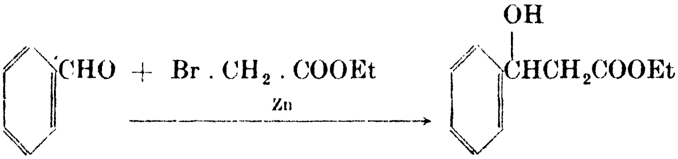
[1] Hlasiwetz, *Ann.*, 1867, **142**, 358.

[2] Winckler, *ibid.*, 1836, **18**, 310.

By the use of sulphur or selenium the α-naphthyl acetic ester or acid can be obtained :—

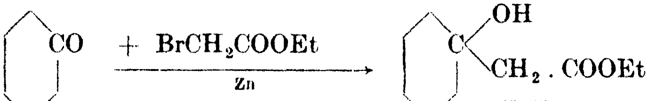


In a similar manner the homologue of mandelic acid can be prepared ; benzaldehyde is reacted with Zn and bromoacetic ester to give[1] β-hydroxy-β-phenylpropionic ester (354).



(354)

Two other important applications are (*a*) the formation of the ester of 1-hydroxy-*cyclo*hexyl acetic acid[2] (355) from *cyclo*-hexanone, and (*b*) the interesting results obtained by Clemo and Ormston[3] with *cyclo*-hexene oxide and *cyclo*-pentanaldehyde, both of which gave the *cyclo*-pentane analogue of (354). Similar results were obtained by Arbuzov,[4] on norpinene oxide.



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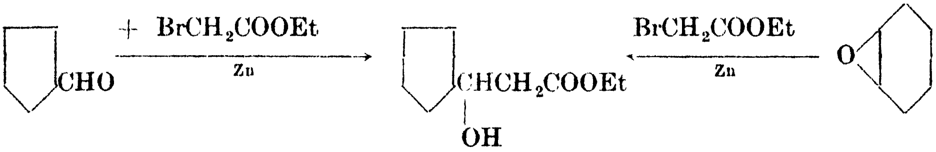

Tropic acid (364) is best synthesised from phenylacetic ester which is condensed with ethyl formate in the presence of sodium ethoxide, giving formphenylacetic ester (357), which readily reduces to tropic ester (358) ; the alternative method from acetophenone (359) *via* atropic acid (362) is shown in formulæ (359) to (364). The occurrence of tropic acid in the solanaceous alkaloids is dealt with in Chapter VII of Vol. II.

Mention must also be made of the reduction of α-keto acids by Clemmensen's reagent (Zn + $HgCl_2$) ; phenylglyoxylic acid[5] is converted to mandelic acid.

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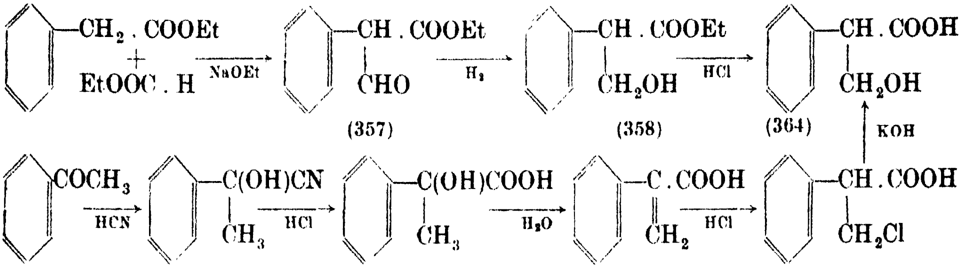
[1] Hauser and Breslow, *Org. Synth.*, 1941, **21**, 51.
[2] Natelson and Gottfried, *J.A.C.S.*, 1931, **61**, 970.
[3] Clemo and Ormston, *J.C.S.*, 1933, 362.
[4] Arbuzov, *J. Gen. Chem.* (U.S.S.R.), 1939, **9**, 255.
[5] Steinkopf and Wolfram, *Ann.*, 1923, **430**, 113.

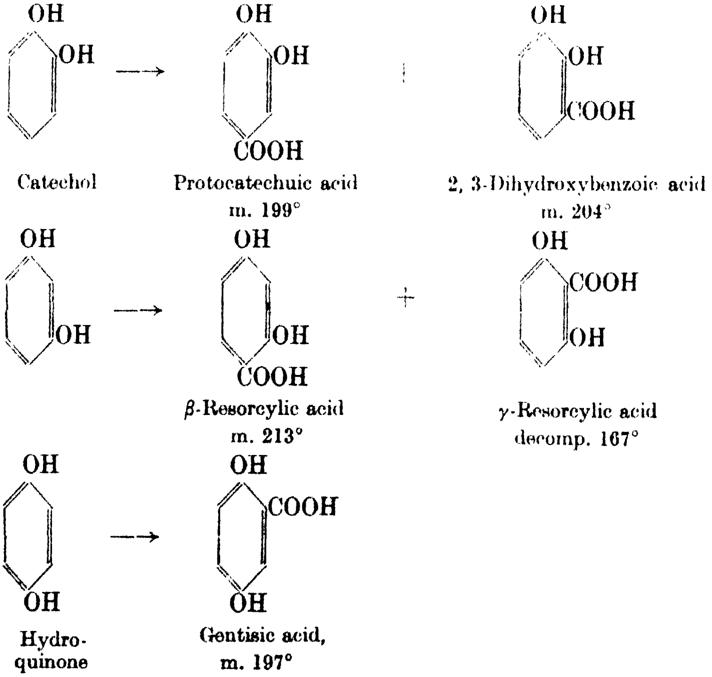
The method is not applicable to β-keto esters, which are reduced to the saturated acid.



(357) (358) (364) (359) (360) (361) (362) (363)

Numerous polyhydroxy acids of this series are known, most of which have been discovered in natural products. Among the dihydroxy acids special reference may be made to protocatechuic acid, the resorcylic acids and to the so-called lichen acids, many of which are derived from orsellinic acid.

The most satisfactory method for preparing the acids of this series is to heat the appropriate dihydric phenol with ammonium carbonate solution in an autoclave at 140°. The ease with which carboxylation takes place contrasts with the strenuous measures required to carboxylate the monohydric phenols. The course of the reactions are shown in the diagram below :—



Catechol

Protocatechuic acid m. 199°

2, 3-Dihydroxybenzoic acid m. 204°

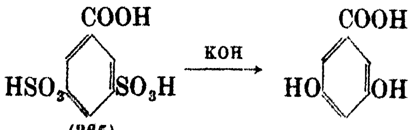
β-Resorcylic acid m. 213°

γ-Resorcylic acid decomp. 167°

Hydro-quinone

Gentisic acid, m. 197°

It will be noted that only one acid of this series—α-resorcylic or 3, 5-dihydroxybenzoic acid, cannot be produced by this method. It is obtained by fusing benzoic disulphonic acid (365) with alkali.



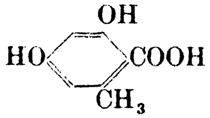
(365)

The simple ethers of protocatechuic acids are frequently met with as degradation products of alkaloids. Thus, vanillic acid, *m*-methoxy-*p*-hydroxybenzoic acid, m. 207° ; veratric acid, 3, 4-dimethoxybenzoic acid, m. 181° and 3, 4-methylenedioxybenzoic acid, piperonylic acid, m. 228°, are often met with in this connexion.

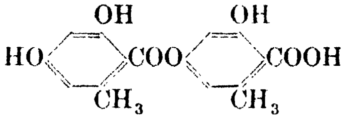
The Lichen Acids.—The lichens constitute an unfailing source of supply of numerous complex aromatic hydroxy acids. The depside group of these acids is derived from hydroxy acids of the orsellinic acid series ; the depsidones are ring compounds with a lactone bridge of great stability ; in addition there is a third class derived from chlorogenic acid and its homologues.

The principal members of the depside group are derived from orsellinic acid and its auto-condensation products, lecanoric and gyrophoric acids, which have the formulæ set out below :—

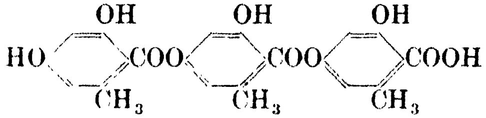
Orsellinic acid



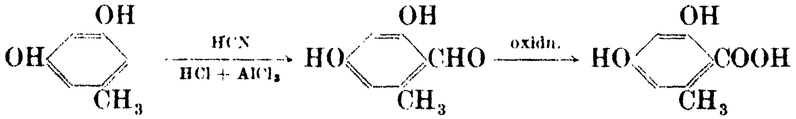
Lecanoric acid



Gyrophoric acid

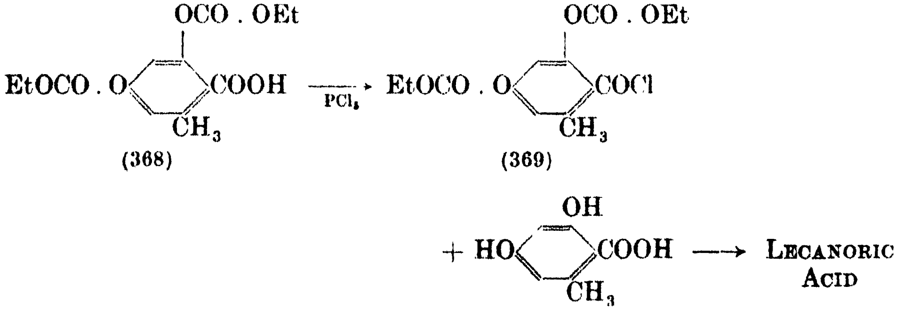


All three of these acids have been synthesised ; the first, orsellinic acid from orcinol, *via* the aldehyde (366), obtained by Gatterman's method and oxidised by permanganate in acetone solution to the acid (367).



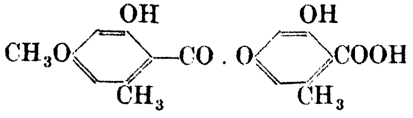
Orcinol (366) (367)

Fischer's synthesis of lecanoric acid commences with orsellinic acid, the hydroxyl groups of which are protected by treatment with ethyl chlorocarbonate, giving



(368) (369)

the substance (368), which yields an acid chloride (369) when warmed with phosphorus pentachloride. This reacts readily with orsellinic acid to give lecanoric acid ester. Evernic acid (370), m. 168–169°, found in many *Evernia* species, is the methyl ether of lecanoric acid.



(370)

These substances are merely illustrative of a whole range of acids in which the starting point is not orcinol, but one of its homologues. These are usually divided into two groups, the orcinol and β-orcinol groups :—

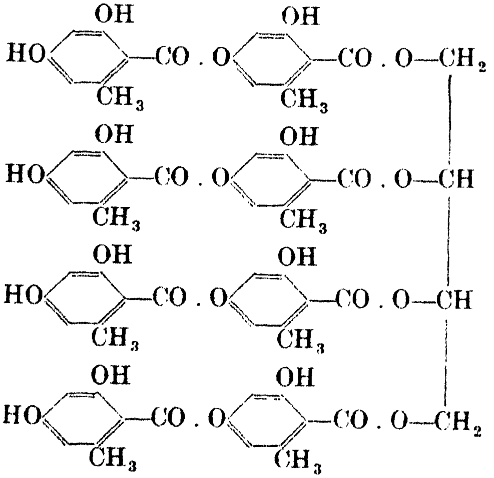
Orcinol Group

2, 4-Dihydroxy-6-methylbenzoic acid	from	orcinol.
2, 4-Dihydroxy-6-*n*-propylbenzoic acid	from	5-propyl resorcinol (Divarinol)
2, 4-Dihydroxy-6-*n*-amylbenzoic acid	from	5-amyl resorcinol (Olivetol)
2, 4-Dihydroxy-6-*n*-heptylbenzoic acid	from	5-heptyl resorcinol
3, 5-Dihydroxy-2-carboxybenzyl-*n*-amyl-ketone	from	3, 5-dihydroxybenzyl, amyl ketone

β-Orcinol (p-Xylorcinol) Group

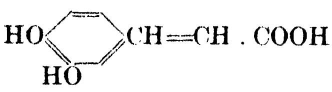
2, 4-Dihydroxy-3, 6-dimethylbenzoic acid	from	2, 5-dimethyl resorcinol
2, 4-Dihydroxy-3-aldo-6-methylbenzoic acid	from	2, 6-dihydroxy-4-methylbenzaldehyde
2, 4, 5-Trihydroxy-3-aldo-6-methyl-benzoic acid	from	2, 3, 6-trihydroxy-4-methylbenzaldehyde
2, 4-Dihydroxy-3-aldo-6-hydroxymethyl-benzoic acid	from	2, 6-Dihydroxy-4-hydroxymethyl-benzaldehyde

In the lichens themselves these depsides are combined with erythritol in the form of tetra esters, e.g., erythrin, or erythritol tetralecanoric ester (371) :—

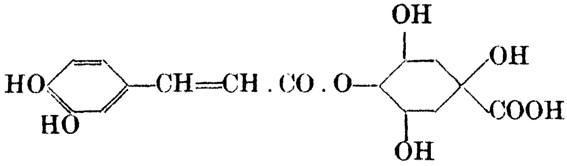


(371) Erythrin

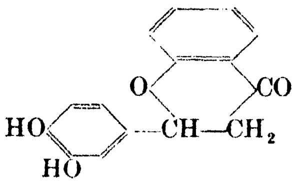
Caffeic acid (372) occurs not only alone in various *Cinchona* species, but as its quinic acid ester in chlorogenic ester, the potassium salt of which is combined with a molecule of caffeine in coffee beans. The name chlorogenic acid (373) is an allusion to the fact that the substance loses hydrogen in the presence of an oxidase to give a deep green pigment, which plays a part in plant metabolism. The name, though apt, is misleading, implying that it might be the chloro- derivative of genic acid. Caffeic acid can also be obtained by the prolonged hydrolysis of eriodictyol (374) which breaks down into phenol and caffeic acid. The two isomeric methyl ethers, hesperitic and ferulic acids, are



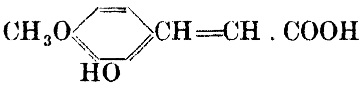
Caffeic acid (372)



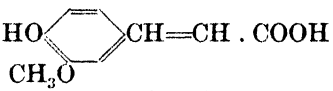
Chlorogenic acid (373)



Eriodictyol (374)

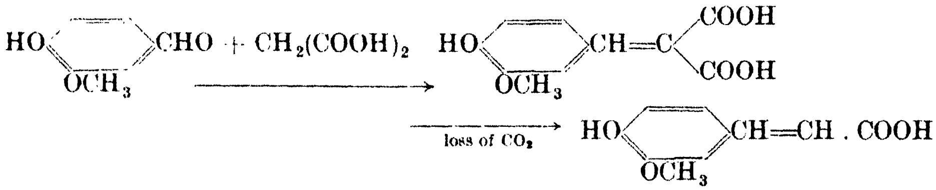


Hesperitic acid



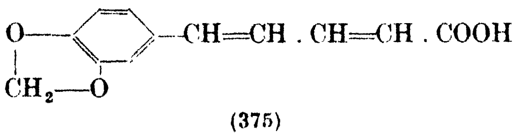
Ferulic acid

related to hesperitin and *homo*eriodictyol in a similar fashion. Ferulic acid can be obtained by the modification of the Perkin reaction in which vanillin is condensed with malonic acid in the presence of piperidine, these reactants being dissolved in pyridine. The reaction takes the course :—



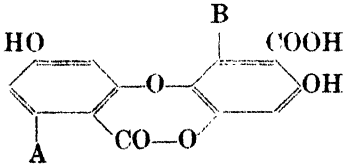
The reaction mixture is allowed to stand at room temperature for three weeks, during which time carbon dioxide is slowly evolved.

Piperic acid, m. 215° (375), may also be regarded as a member of this family of substances. It is obtained by hydrolysis of the alkaloid piperine, which is its piperidide.

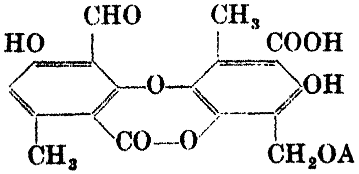


(375)

The so-called depsidones are, fundamentally, derivatives of diphenyl ether ; the skeletons most commonly encountered are

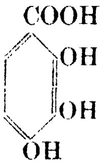


$A = B = CH_2COC_5H_{11}$	Alecturonic acid
$A = CH_2 . COC_5H_{11} ; B = C_5H_{11}$	Physodic acid



$A = H$	Protocetraric acid
$A = C_2H_5$	Cetraric acid
$A = CO . CH = CH . COOH$	Fumarcetraric acid

Of the trihydroxy acids of the aromatic series, gallic acid (379) is the most important. It is very widely distributed naturally in the form of tannins, which are the subject of an Appendix to this chapter. Gallic acid itself was prepared by Scheele by allowing an aqueous extract of galls to stand in a warm place, and frequently breaking up the crust of mould which formed. A crystalline precipitate developed which on recrystallisation proved to be gallic acid. Ordinary yeast will also break down the tannins to gallic acid (379). The formation of gallic acid by fusion of 4-bromo-α-resorcylic acid with alkali indicates its structure as 3, 4, 5-trihydroxybenzoic acid. The main use of gallic acid is for ink manufacture. Ink is a dilute solution of ferrous sulphate and gallic acid in very dilute sulphuric acid, to which a colloid such as gum has been added. When used, the sulphuric acid is neutralised by the loading of the paper and the ferrous salt is soon oxidised to the ferric state in which condition it reacts with gallic acid to form a deep blue-black precipitate. A blue dye is often added to ink to provide a temporary colour until the iron gallate has been formed.



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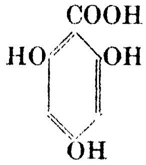

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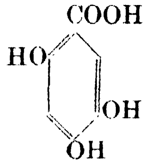

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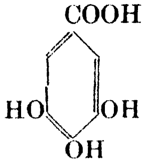
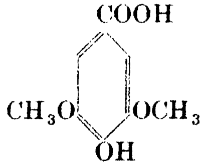
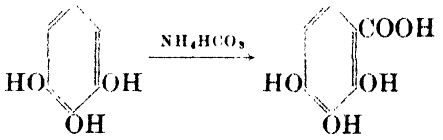


(379)

Gallic acid forms needles, m. 222°; apart from digallic acid and the tannins its commonest natural derivative is syringaic acid, the 3, 5-dimethyl ether (380); it has already been discussed in connexion with the anthocyanins.



(380)



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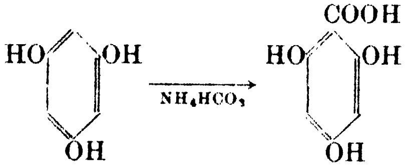
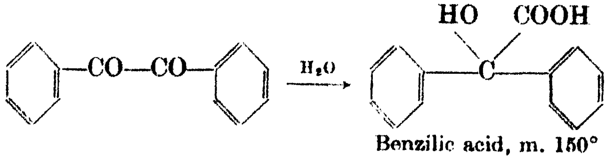


(382)

The other acids of the series are prepared by heating the appropriate trihydric phenol with ammonium bicarbonate solution under pressure (see 381 to 382).

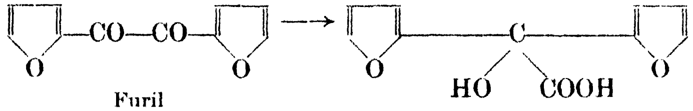
Benzilic Acids

When benzil is fused with potash, or its solution in potash is subjected to a stream of air, a reaction takes place which is apparently deep-seated, since a disturbance of the link between the two rings takes place, benzilic acid being formed. Although the reaction may be formulated :—



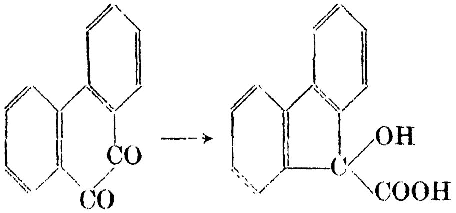
Benzilic acid, m. 150°

this postulates nothing concerning the general course of the reaction. The reaction is a general one, anisil and cuminil give the reaction, as also does furil :—



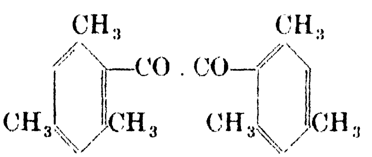
Furil Furilic acid

Surprisingly enough, the reaction is possible with phenanthrenequinone :—

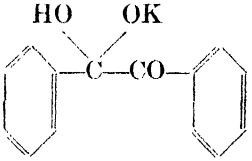


(383)

which gives diphenylene glycollic acid (383) on caustic fusion. On the other hand, Kohler and Baltzly [1] showed that hexamethylbenzil (384) from mesityl aldehyde, did not give a ' benzilic ' acid ; an observation which led them to suppose that the inhibition was due to steric conditions preventing the addition



(384)



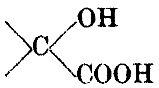
(385)

of reagents to the carbonyl group. This appears to be confirmed by the work of Scheuing,[2] who found that on mixing solutions of benzil and potassium hydroxide in pyridine a compound of definite composition separated, $C_{14}H_{10}O_2 . KOH$. This substance, which was formulated as in (385), slowly rearranged to potassium benzilate even at 0° ; at 80° the rearrangement was rapid.

Alicyclic Hydroxy Acids

A number of hydroxy acids of the *cyclo*hexane series are of interest as substances of natural occurrence. Reference has already been made to quinic acid, and as this substance is so widely distributed in plants its constitution becomes of importance. The empirical formula, $C_7H_{12}O_6$ may be subdivided into $C_6H_7(OH)_4COOH$, since it has all the properties of a carboxylic acid, and the presence of four hydroxyl groups can be demonstrated by alkylation. The fact that quinic acid can readily be oxidised to aromatic compounds leads us to suppose that it is a tetrahydroxy *cyclo*-hexanecarboxylic acid.

Further light is thrown on the problem of the structure of quinic acid by the following points :—

(1) With strong sulphuric acid carbon monoxide is evolved (cf. citric and furilic acids) pointing to a  $>C{<}^{OH}_{COOH}$ group ; hence it is deduced that one hydroxyl is attached to the same carbon atom as the carboxyl group.

---

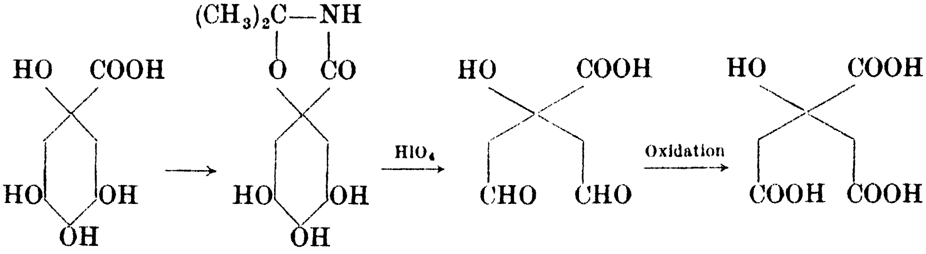
[1] Kohler and Baltzly, *J.A.C.S.*, 1932, **54**, 4019.

[2] Scheuing, *Ber.*, 1923, **56**, 252.

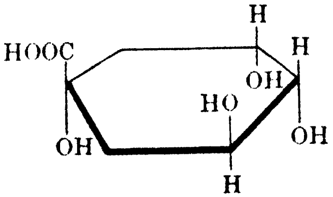
(2) Quinic acid is easily converted to protocatechuic acid; hence two of the hydroxyl groups must occupy positions '3' and '4' to the carboxyl.

Thus, quinic acid appears to be a 1, 3, 4-trihydroxy *cyclo*hexane carboxylic acid, with an additional hydroxyl group in a position as yet undecided.

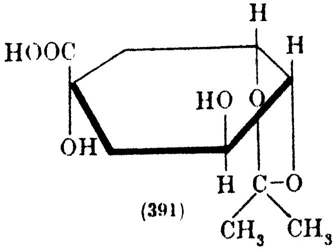
(3) The position of the fourth hydroxyl group is ascertained by the following steps. The amide of quinic acid (386) forms an acetone compound (387) which is oxidised by periodic acid to the dialdehyde of citric acid (388); from the dialdehyde, citric acid (389) itself may be obtained and characterised. This proves that the two groups on either side of the carbon carrying the carboxyl group are unsubstituted methylene groups and confirms the formula of quinic acid as (386).



(386) Quinic acid (387) (388) Citric dialdehyde (389) Citric acid



(390)



(391)

The stereochemical pattern of quinic acid proves to be that shown in (390). This conclusion is arrived at as follows:—

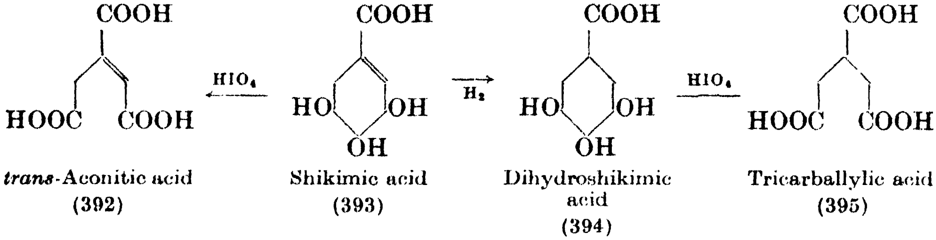
(1) Quinic acid forms an acetone compound with a five-membered ring, by loss of the elements of water. This can only happen from a *cis*-dihydroxy structure in which the hydroxyl groups are on adjacent carbon atoms. This structure (391) shows that at least two of the trio of hydroxyl groups in the 3, 4, 5-positions are on the same side of the ring.

(2) The acetone compound of quinic acid can form a lactone. Hence, whichever side the third hydroxyl group of the trio is on (in relation to the other two), so also is the carboxyl group, since *trans*-lactones are unstable.

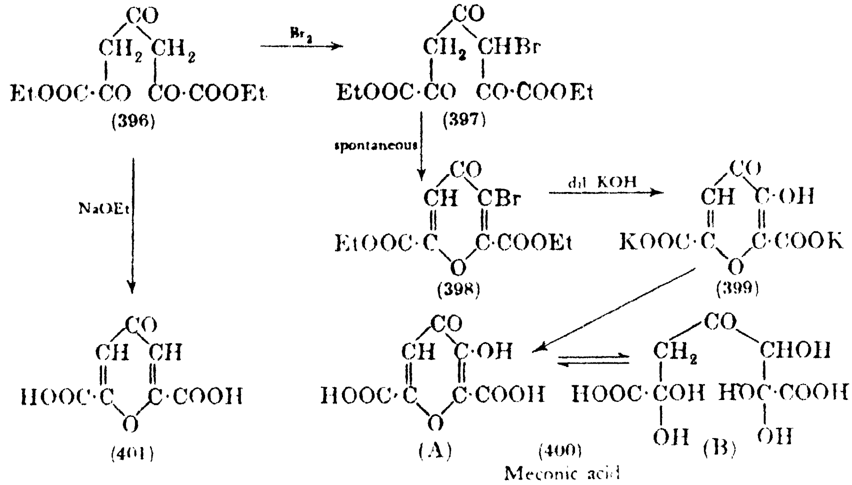
(3) 3-Methyl quinic acid cannot form a lactone; hence the third hydroxyl group must be *trans*- to the other two and quinic acid must have the stereochemical structure shown in (390).

Shikimic acid (393) is closely related to quinic acid, being obtained by the loss of the elements of water from the 1-hydroxyl and the adjacent methylene group of quinic acid. It can readily be converted to a dihydro derivative (394); the latter can be converted by oxidation with periodic acid to tricarballylic acid (395); shikimic acid itself gives *trans*-aconitic acid (392).

Meconic acid has been known over a century since Setürner [1] in 1828, during his researches on opium (the Greek Μηκώνιον, gives rise to the name of the acid) observed the acid as a by-product in the preparation of the alkaloid. It gives a characteristic blood red colour with ferric chloride (not discharged, as is ferric thiocyanate, by gold chloride). The synthesis of meconic acid followed nearly a hundred years later ; [2]



trans-Aconitic acid (392) Shikimic acid (393) Dihydroshikimic acid (394) Tricarballylic acid (395)

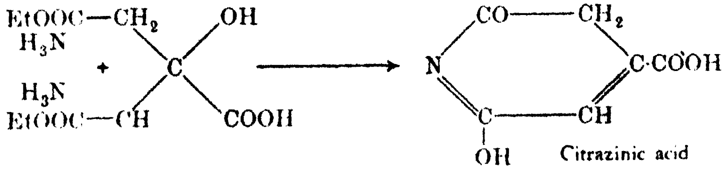


(396) (397) (398) (399) (401) (A) (400) (B) Meconic acid

Ethyl acetonyldioxalate (396) on treatment with bromine passes spontaneously through the monobromo ester (397) to ethyl 3-bromochelidonate (398) ; this on careful removal of the bromine and replacement by hydroxyl, using dilute potassium hydroxide solution, gives potassium meconate (399). The ring and open formulæ for meconic acid are shown side by side in (400) ; so far no certain decision has been made as to which more correctly represents the true structure of the acid.

Chelidonic acid, taking its name from the celandine (*Chelidonus majus*) from which it was isolated in 1839 by Probst,[3] has the structure of meconic acid without the hydroxyl group. It may be synthesised from acetone and ethyl oxalate in the presence of sodium ethoxide as indicated in (401).

The inter-relations of this group of acids is shown in Table XL. These acids, as well as citric and malic acids, are all capable of giving pyridine derivatives with ammonia ; thus, citric ester and ammonia react :—



Citrazinic acid

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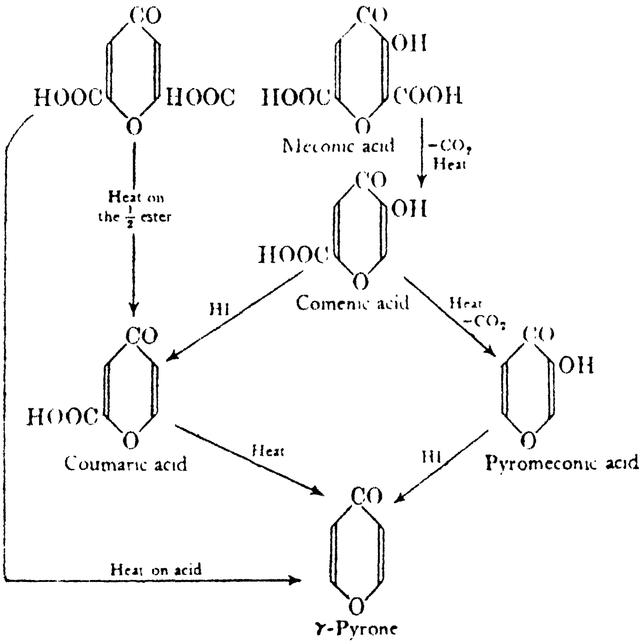
[1] Setürner, *Pogg. Ann.*, 1828, **13**, 1, 234.

[2] Thoms and Pietrulla, *Ber. deut. Pharm. Ges.*, 1921, **31**, 4.

[3] Probst, *Ann.*, 1839, **29**, 116.

It is thought that these acids are derived *in vivo* from simple units such as formaldehyde and water, and that by reaction with ammonia, they give cyclic nitrogen compounds from which the alkaloids are evolved.

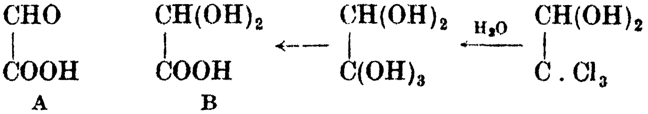
TABLE XL



ALDEHYDE ACIDS

Not many aldehyde acids are commonly met with ; the simplest is glyoxylic acid. It occurs naturally in the juices of plants and in unripe fruits from which it disappears as the sugar content increases from which it is surmised that it may play a part in the synthesis of sugars.

It can be made from dichloro- or dibromoacetic acid by boiling with water or silver carbonate. It has also been obtained by the oxidation of alcohol, glycol, glycollic acid and by the electrolytic reduction of oxalic acid. The persistence with which it retains its molecule of crystal-water lends support to the view that it, like chloral, exists as a polyhydroxy compound (Formula B (402)). It may be added that glyoxylic acid can also be obtained by heating

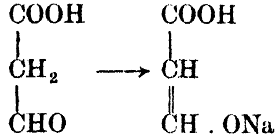


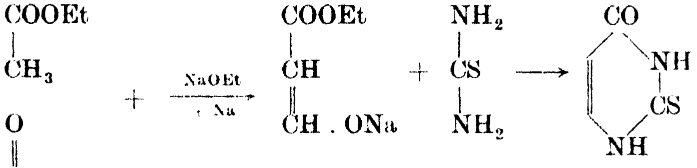
$$\underset{A}{\begin{array}{l}CHO\\|\\COOH\end{array}} \qquad \underset{B}{\begin{array}{l}CH(OH)_2\\|\\COOH\end{array}} \longleftarrow \begin{array}{l}CH(OH)_2\\|\\C(OH)_3\end{array} \xleftarrow{H_2O} \begin{array}{l}CH(OH)_2\\|\\C\,.\,Cl_3\end{array}$$

(402) (403)

a solution of chloral hydrate (403) under pressure. Glyoxylic acid forms rhombic prisms which are volatile with steam. It gives salts as an acid, but gives also all the characteristic reactions of an aldehyde.

The half aldehyde of malonic acid is the active agent in the v. Pechmann coumarin synthesis in which malic and sulphuric acids are allowed to act upon a polyhydric phenol (p. 608). It does not seem likely that the free aldehyde exists, although the sodium derivative of the enolic form of the ester (404) is known and is a most useful synthetic reagent ; condensing with urea to form uracil, and with thiourea to give thiouracil (405), a drug used in controlling the basal metabolic rate of the condition known as thyrotoxicosis. The ester is

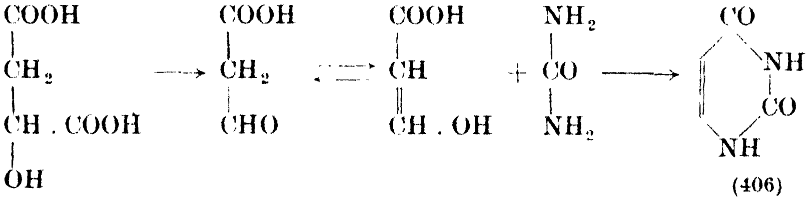




(404)

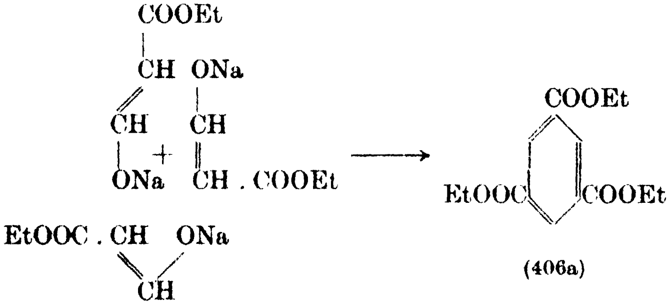
(405)
THIOURACIL

often called formylacetic ester. It will be observed that the formation of uracil (406) from malic acid and urea in the presence of sulphuric acid is essentially a condensation of the half aldehyde of malonic acid, in the enol condition :—



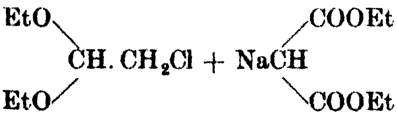
(406)
Uracil

If the sodium derivative of formylacetic ester is acidified, the alcohol (or aldehyde) immediately trimerises to benzene 1, 3, 5-tricarboxylic ester (406a).

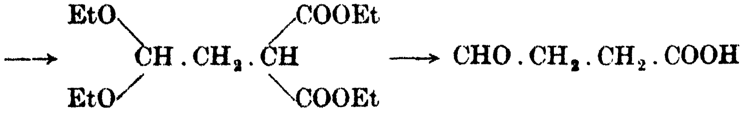


(406a)

A useful general method for preparing the half-aldehydes of the higher dibasic acids is to commence with a chloroacetal (407) which is allowed to react with sodio-malonic ester yielding a product of the structure (408) ; this on

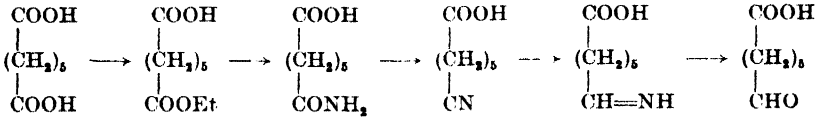


(407)



(408)

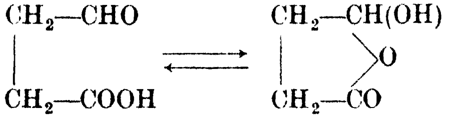
alkaline hydrolysis in the cold yields the acid which on boiling in water loses carbon dioxide and alcohol, the half aldehyde being produced. An alternative method suitable for the longer chain dibasic acid is to react the half ester with ammonia to the half amide and to convert this by controlled action of hypochlorite solution to the cyanide. This can then be reduced to the imine and



$$\begin{array}{c}COOH\\|\\(CH_2)_5\\|\\COOH\end{array} \longrightarrow \begin{array}{c}COOH\\|\\(CH_2)_5\\|\\COOEt\end{array} \longrightarrow \begin{array}{c}COOH\\|\\(CH_2)_5\\|\\CONH_2\end{array} \longrightarrow \begin{array}{c}COOH\\|\\(CH_2)_5\\|\\CN\end{array} \dashrightarrow \begin{array}{c}COOH\\|\\(CH_2)_5\\|\\CH{=}NH\end{array} \longrightarrow \begin{array}{c}COOH\\|\\(CH_2)_5\\|\\CHO\end{array}$$

(409)

the aldehyde obtained by simultaneous hydrolysis (409). In the case of the half-aldehyde of succinic acid, the aldehyde is an equilibrium with its internal acetal (410); the higher aldo-acids are quite normal in their structure and



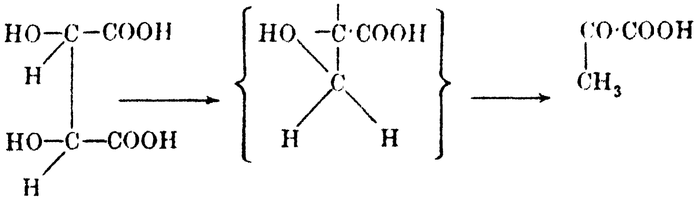
(410)

behaviour. Many of them have been prepared during the oxidative breakdown of the higher unsaturated acids. Thus, the half-aldehyde of azelaic acid, $HOOC(CH_2)_7CHO$, has been obtained from oleic acid, and the half-aldehyde of adipic acid, $HOOC(CH_2)_4CHO$, from arachidonic acid.

KETONIC ACIDS

The simplest keto-acid is *pyruvic acid*. Discovered in early times by distilling tartaric acid and called ' spiritus tartari '; Paracelsus ascribed medicinal properties to the crude form, and Guyton de Morveau in the eighteenth century examined the crude material and separated from it what he claimed to be the new acid—' pyrotartaric acid '. As usual, Fourcroy and Vauquelin dismissed the substance as ' impure ' acetic acid, and it remained for Valentine Rose in 1807 to demonstrate the individual nature of the material, and for Berzelius [1] in 1836, to distinguish it from another acid already termed pyrotartaric. The new acid was re-named pyruvic acid.

No better method than the distillation of tartaric acid, either alone or with sodium bisulphate, has been so far devised for the production of pyruvic acid:—



The distillate must be fractionated *in vacuo* immediately and the fraction distilling between 68° and 70°/20 mm. collected as pyruvic acid. It is a colourless liquid with a characteristic empyreumatic smell, m. 17°; b. 165°; on standing it polymerises.

Several alternative methods of preparation are known, which serve to demonstrate the constitution of pyruvic acid. Acetyl cyanide (from acetyl chloride and silver cyanide) is allowed to stand in concentrated hydrochloric acid when pyruvic amide separates. This is readily hydrolysed to the acid

---

[1] Berzelius, *Pogg. Ann.*, 1835, **36**, 1.

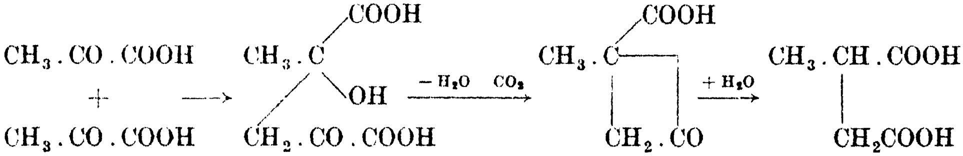
$$CH_3COCN \longrightarrow CH_3COCONH_2 \longrightarrow CH_3COCOOH$$

itself. Attempts to hydrolyse acetyl cyanide directly to the acid usually result in the removal of hydrogen cyanide and the regeneration of acetic acid. Pyruvic acid is also formed when α, α-dichloropropionic acid is heated with dilute alkalies, or, preferably, silver oxide :—

$$CH_3CCl_2\,.\,COOH + Ag_2O \longrightarrow CH_3COCOOH + 2AgBr$$

It is usually more convenient to make α, α-dichloropropionic acid by heating pyruvic acid with phosphorus pentachloride.

In chemical properties, pyruvic acid demonstrates actively both the acid and keto group. It forms a fairly insoluble phenylhydrazone and may be used to liberate sugars from their phenylhydrazones, since the latter are usually more soluble than that of pyruvic acid. It is decomposed by concentrated sulphuric acid to carbon monoxide and acetic acid, a reaction which is characteristic of α-keto acids. Pyruvic acid plays an important part in the biodegradation of sugars, and further references will be made to it in this connexion. Pyruvic acid tends to pass into methyl succinic acid on standing in aqueous solution, or warming with very dilute hydrochloric acid ; the reaction is not clearly understood, but may take the following course :—



Acetoacetic acid, CH_3COCH_2COOH, is unstable, decomposing almost instantaneously into carbon dioxide and acetone. The ester is easily obtained, and is discussed with other esters exhibiting the active methylene group in Appendix II of this chapter. Swarts[1] has shown that trifluoroacetoacetic acid is quite stable and can be distilled without change at ordinary pressure. This unusual property is not due to any abnormality of structure, since the trifluoro acid gives trifluoroacetone by heating with alkalies in the usual way, and may be prepared normally from ethyl trifluoroacetate, ethylacetate and sodium ethoxide in the normal manner :—

$$CF_3\,.\,COOEt + CH_3\,.\,COOEt \xrightarrow[\text{NaOEt}]{} CF_3\,.\,CO\,.\,CH_2\,.\,COOEt$$
$$\xrightarrow{\text{HCl}} CF_3\,.\,CO\,.\,CH_2\,.\,COOH$$

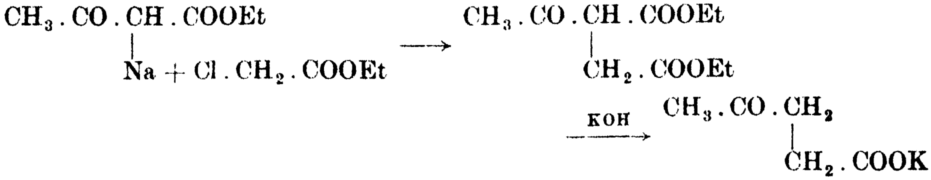
Lævulic acid, $CH_3COCH_2CH_3COOH$, was originally prepared by Tollens by boiling sucrose with dilute sulphuric acid, where it appears to be formed by a breakdown of lævulose ;[2] the steps by which this transformation proceeds are unknown. Lævulic acid is also a product of the hydrolysis of a number of naturally occurring products derived from the isoprene unit ; thus Harries obtained it, together with its aldehyde, from the hydrolysis of rubber ozonide.

Various syntheses are available, such as the interaction of chloroacetic ester and the sodio derivative of acetoacetic ester, whereby a di-acid ester is obtained which on heating with caustic alkali breaks down into the alkali salt of lævulic acid.

---

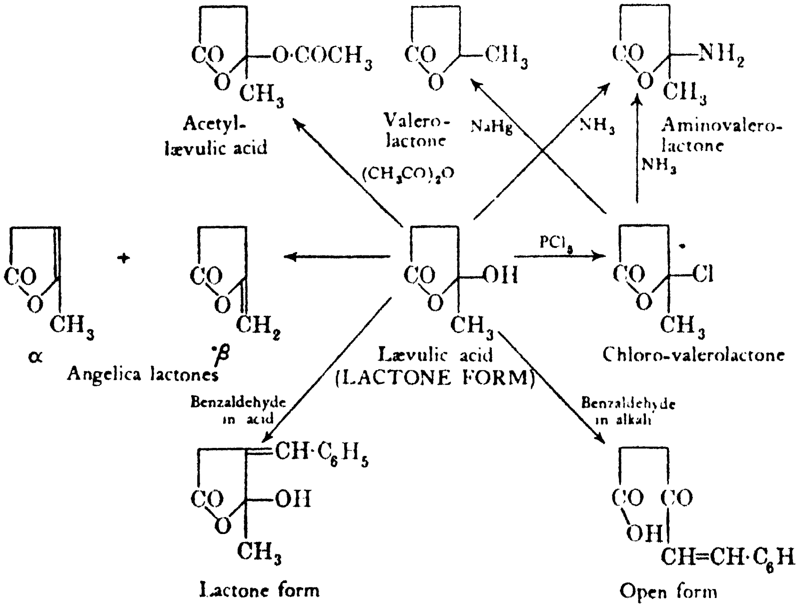
[1] Swarts, *Bull. acad. roy. Belg.*, 1926, **12**, 679, 692, 721 ; *Bull. soc. chim. Belg.*, 1926, **35**, 411 ; 1927, **36**, 313, 323.

[2] Tollens and Grote, *Ann.*, 1881, **206**, 226.

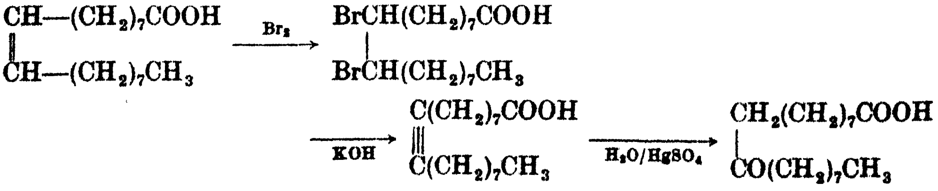


$$\begin{array}{l} CH_3.CO.CH.COOEt \\ \quad\quad\quad | \\ \quad\quad\ Na + Cl.CH_2.COOEt \end{array} \longrightarrow \begin{array}{l} CH_3.CO.CH.COOEt \\ \quad\quad\quad | \\ \quad\quad\ CH_2.COOEt \end{array} \xrightarrow{KOH} \begin{array}{l} CH_3.CO.CH_2 \\ \quad\quad\quad | \\ \quad\quad\ CH_2.COOK \end{array}$$

The reaction is a general one, and is capable of being used for a wide range of substituted lævulic acids. Lævulic acid is stable, and can be distilled at 250° without decomposition. It passes on prolonged heating into an intramolecular hydroxy-lactone; indeed, it often reacts in this capacity, giving with acetic anhydride a crystalline acetate and with phosphorus chloride, chlorovalerolactone instead of the expected acid chloride, whilst when maintained below the boiling point for some hours it is converted to a mixture of the angelica lactones. These reactions are summarised in the diagram below :—

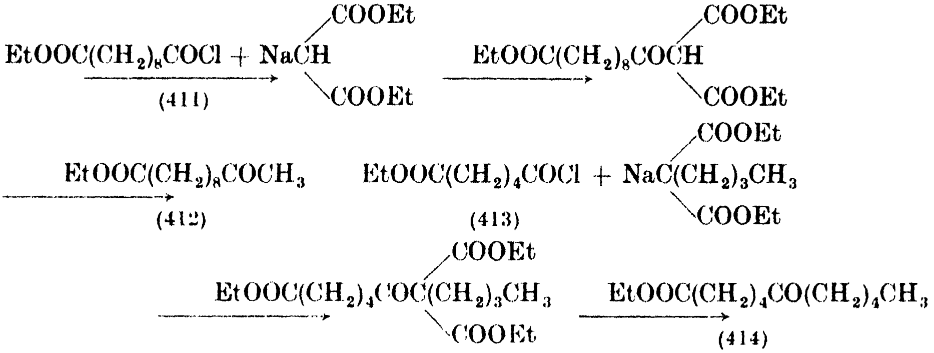


Many other ketonic acids are known, and a few are mentioned in Table XLI. The general methods for preparing them (apart from those already described) are: The bromination of an unsaturated acid, e.g., oleic, followed by removal of the bromine to give an acetylenic analogue of the acid. This will then add on the elements of water when treated with mercuric sulphate in sulphuric acid. The carbonyl group is formed as far away from the carboxyl group as possible.



$$\begin{array}{l} CH—(CH_2)_7COOH \\ \| \\ CH—(CH_2)_7CH_3 \end{array} \xrightarrow{Br_2} \begin{array}{l} BrCH(CH_2)_7COOH \\ \quad | \\ BrCH(CH_2)_7CH_3 \end{array} \xrightarrow{KOH} \begin{array}{l} C(CH_2)_7COOH \\ \equiv \\ C(CH_2)_7CH_3 \end{array} \xrightarrow{H_2O/HgSO_4} \begin{array}{l} CH_2(CH_2)_7COOH \\ | \\ CO(CH_2)_7CH_3 \end{array}$$

They can also be obtained from the half ester-chloride of dibasic acids. Thus, if the half ester-chloride of sebacic acid (411) is condensed with sodiomalonic ester, a ketonic tribasic ester is formed which, on hydrolysis loses, owing



$$\underset{(411)}{EtOOC(CH_2)_8COCl} + NaCH(COOEt)_2 \longrightarrow EtOOC(CH_2)_8COCH(COOEt)_2 \longrightarrow \underset{(412)}{EtOOC(CH_2)_8COCH_3}$$

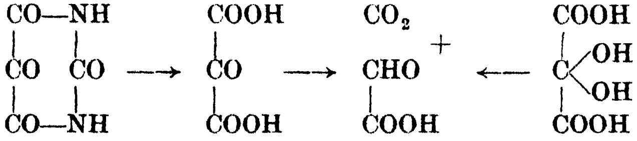
$$\underset{(413)}{EtOOC(CH_2)_4COCl + NaC(COOEt)_2(CH_2)_3CH_3} \longrightarrow EtOOC(CH_2)_4COC(COOEt)_2(CH_2)_3CH_3 \longrightarrow \underset{(414)}{EtOOC(CH_2)_4CO(CH_2)_4CH_3}$$

to the proximity of the ketone group, two acid groups from the malonic carbon atom leaving undecanone-10, acid (412). By using the ester-chloride of adipic acid and sodio-*n*-butylmalonic ester (413) the isomeric undecanone-5, acid (414) can be prepared. In this way, numerous keto acids can be prepared of almost any desired structure.

TABLE XLI

Acid	Formula	Properties
Mesitonic (α, α-Dimethyl lævulic)	$CH_3 . CO . CH_2C(CH_3)_2COOH$	From mesityl oxide and potassium cyanide
Hexanone-5 (δ-ketocaproic)	$CH_3 . CO(CH_2)_3COOH$	The next homologue of lævulic
Lactaric	$CH_3(CH_2)_{11}CO(CH_2)_4COOH$	From tariric acid, by the addition of water
Geronic	$CH_3CO(CH_2)_3C(CH_3)_2COOH$	(See under 'Terpenes')
Undecanone-10	$CH_3CO(CH_2)_8COOH$	Myddleton and Barrett, *J.A.C.S.*, 1927, **49**, 2258

There are one or two ketonic dibasic acids which have importance in connexion with structural problems. Thus, mesoxalic acid (416) is closely related to the elucidation of the uric acid structure. It is obtained from its ureide alloxan (415) which is, in turn, obtained by oxidising uric acid. It was from



(415) (416) (417) (418)

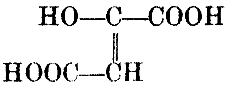
alloxan that Liebig and Wohler[1] first obtained mesoxalic acid in 1838. To prepare the acid, alloxan is heated in warm aqueous solution with one equivalent of baryta, which forms the barium salt of the open-chain alloxan structure. The salt is cooled, filtered off, washed and 200 g. are boiled with 20 litres of water for ten minutes and the solution rapidly cooled. Barium mesoxalate crystallises. Both mesoxalic acid and its ester obstinately retain one molecule of water which is probably attached as in the formula (418). On heating, it loses carbon dioxide and is converted to glyoxylic acid (417).

---

[1] Liebig and Wohler, *Ann.*, 1838, **26**, 298.

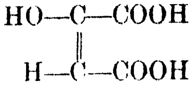
The next highest homologue of mesoxalic acid is oxalacetic acid, which may be considered with the diketo derivative—the so-called dihydroxytartaric acid.

The ester of this acid is readily prepared by the condensation of ethyl oxalate and ethyl acetate. This ester will be more fully dealt with in Appendix II of this chapter. The free acid is more difficult to prepare ; Fenton's method is to oxidise malic acid with hydrogen peroxide in the presence of ferrous sulphate Oxalacetic acid appears to exist in the completely enolised forms (419) and (420) which were isolated by Wöhl and which are, in consequence of their structure, named hydroxyfumaric and hydroxymaleic acids.



$$\begin{array}{r}\text{HO—C—COOH}\\ \Vert\quad\\ \text{HOOC—CH}\quad\end{array}$$

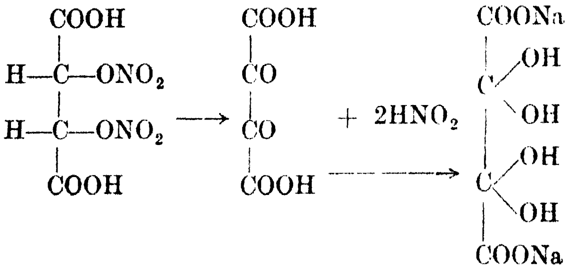
m. 184° (419)



$$\begin{array}{l}\text{HO—C—COOH}\\ \quad\Vert\\ \text{H—C—COOH}\end{array}$$

m. 152° (420)

Dihydroxytartaric Acid.—The treatment of tartaric acid with nitric and sulphuric acids leads to a dinitrate (421), analogous to di-nitroglycol, trinitroglycerol and tetranitro-erythritol. This nitrate gradually decomposes when held in solution and on pouring on to ice and adding salt the sparingly soluble sodium salt of dihydroxytartaric acid separates (422).



(421) (422)

Dihydroxytartaric acid is also formed by the action of nitrous acid on catechol. The mechanism of the change is obscure. The acid itself forms small deliquescent crystals which are unstable and which, on keeping, decompose into tartronic acid and carbon dioxide ; it is this instability which militates against the use of dioxytartaric acid as an analytical reagent for sodium. The test was introduced by Fenton in 1898,[1] and depends on the fact that sodium dihydroxytartrate is soluble in water at 0° only to the extent of 4 parts in 10,000. The reaction has been further studied by Okatov.[2] Although like other compounds of this type, dihydroxytartaric acid obstinately retains its water and is formulated by some according to the structure (422), it nevertheless gives the reactions of a diketone, forming an osazone, which is used for detecting minute traces of calcium ; with it distilled water which is contaminated with 3–5 per cent. of tap water can be made to give a positive reaction.

Industrially, dihydroxytartaric acid, in the form of its sodium salt, was at one time largely produced for the preparation of the dyestuff Tartrazine.* Two molecules of phenylhydrazine sulphonic acid are allowed to react with one of dihydroxy tartaric acid,[3] when the condensation depicted on p. 629 takes place. Tartrazine is still manufactured in modest quantities, as it affords a fine fast wool yellow.

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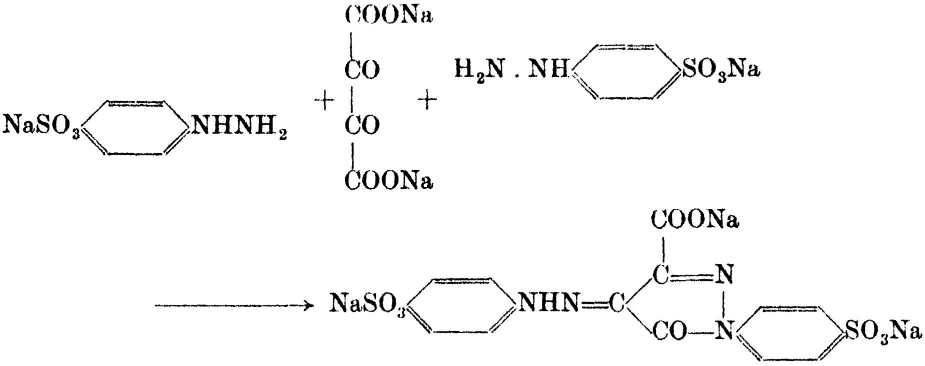
[1] Fenton, *J.C.S.*, 1898, **73**, 71, 167 and 472.

[2] Okatov, *J. Russ. Phys. Chem. Soc.*, 1928, **60**, 661.

[3] Ziegler, *Ber.*, 1887, **20**, 834.

* Tartrazine dyes and their formation are exhaustively described in Cohn " Die Pyrazolonfarbstoffe ", Stuttgart, 1910.



TARTRAZINE (423)

Amongst the ketonic dibasic acids, acetone dicarboxylic acid occupies a special place ; it is one of the most easily available representatives of the series and has two active methylene groups, so that its ester (q.v.) is of considerable synthetic value. The formation from citric acid has been discussed (see p. 604) ; the acid forms small needles. Whilst many other keto-acids are known, few of them have properties which need to be described here ; some, like Balbiano's acid (α, β, β-trimethyl keto glutaric acid) are discussed under other headings (e.g. terpenes).

THE CROCONIC ACID FAMILY

The inclusion of this family under the heading of the acids is scarcely justified on structural grounds, as they have no —COOH group ; it is, however, convenient to discuss them here, especially in view of their well-defined salts. Curiously enough, when rhodizonic acid was first prepared it was named ' carboxylic acid ' ; but this name was changed when the former was appropriated for the characteristic group of organic acids.

It had been known for some time, in 1825, that when potassium was prepared by Brunner's method an explosive substance occasionally made its appearance. Berzelius and Wöhler[1] examined this product and found it to be a greyish porous mass which, on standing in the air, turned green and deliquesced to a liquid mass which on standing, or dilution with water, gave a yellow solution and a scarlet red precipitate. The yellow solution gave on evaporation gold scales of potassium croconate (κροκόν = saffron), and the precipitate proved to be the salt of a new acid, rhodizonic acid (ροδιζω = rose red colour).

Liebig[2] was much attracted by these compounds, and studied them closely, since he was studying carbon monoxide as a ' radicle ', and had found it to be related to carbonic acid and oxalic acid which were its oxidation products, and to phosgene, its chloride. Realising that the new compounds resulted from the reaction of carbon monoxide on potassium, Liebig found in them a confirmation of his conception of carbon monoxide as a radicle ; as he put it " In the pursuit of this idea I have arrived at most remarkable and interesting results, which would seem to prove that these resemblances are not confined to the compounds just described." Brodie made a careful study of the action of potassium on carbon monoxide, and showed that the absorption was slow until the grey porous product was formed, but that after this stage it was rapid until the $(COK)_n$ was obtained as a dark red explosive mass. The scheme of decompositions following the absorption of carbon monoxide by potassium are shown in the left-hand column of Table XLII. The substance $(COK)_6$ is undoubtedly the hexa-potassium derivative of hexahydroxybenzene (424) and

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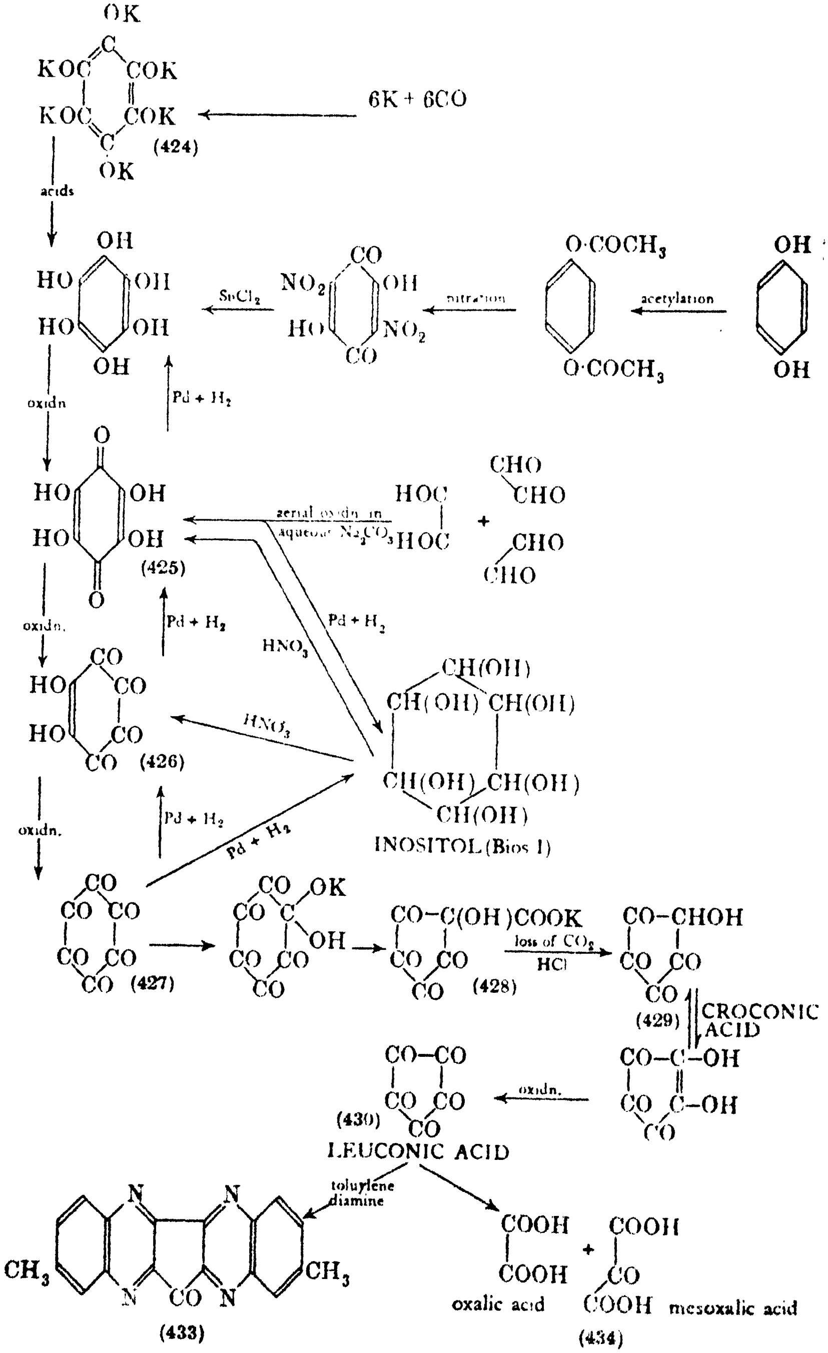
[1] Berzelius and Wöhler, *Pogg. Ann.*, 1825, **4**, 31.

[2] Liebig, *Ann.*, 1834, **11**, 182.

TABLE XLII

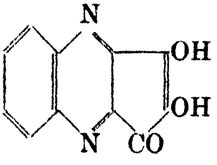


on gradual oxidation it passes through the stages of tetrahydroxyquinone (425), rhodizonic acid (426) and finally to *cyclo*hexane hexa-one (427). These stages can be followed practically, and in many cases alternative methods are available for their preparation. Thus hexahydroxybenzene can be prepared by commencing with hydroquinone and acetylating its hydroxyl groups. On nitrating the diacetyl compound, oxidation and nitration proceed together and the substance dinitrodihydroxy quinone (nitranilic acid) is obtained. On stannous chloride reduction this acid is reduced to a diaminotetrahydroxybenzene (not shown in the diagram) which loses ammonia readily giving hexahydroxybenzene. The latter can be isolated as white needles in the absence of air, which is rapidly absorbed by solutions of the hexahydroxybenzene, yielding violet solutions of tetrahydroxyquinone. The hexahydroxybenzene yields a normal hexaacetyl compound, m. 203°, and crystallising in rhombic prisms. When solutions of hexahydroxybenzene, tetrahydroxyquinone, rhodizonic acid or triquinoyl are reduced with palladium and hydrogen, inositol is formed ; on the contrary, when inositol is oxidised with nitric acid at 100°, Maquenne[1] was able to show the formation of tetrahydroxyquinone and rhodizonic acid.

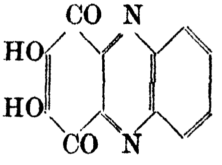
The two latter substances are most easily prepared by the method of Homolka[2] in which glyoxal or its bisulphite compound is oxidised in sodium carbonate solution at 50° with a current of air. Tetrahydroxyquinone forms almost black needles with a green reflex, as also does its di-sodium derivative, the compound most commonly encountered. Rhodizonic acid forms a colourless monohydrate,[3] which, on loss of the water of crystallisation, is converted to a black micro-crystalline powder.

The acid sodium salt is a red powder. The two compounds, tetrahydroxy quinone and rhodizonic acid are valued for their brilliant red barium salts which not only serve to detect minute amounts of barium ($0{\cdot}25\gamma$ in one drop ; with disodium rhodizonate), but also act as indicators in the titration of sulphuric acid with barium solutions ; a solution of sulphuric acid or sulphate, coloured pale yellow by rhodizonic acid may be titrated with barium chloride solution, until the sudden change to red indicates the presence of excess barium ion.

When any of the foregoing substances is allowed to stand in alkaline solution, it becomes oxidised to triquinoyl which undergoes a benzilic acid rearrangement involving one molecule of alkali, giving the potassium salt of an acid (428) which when acidified loses carbon dioxide to give croconic acid (429), a tautomeric substance, existing mainly in the dihydroxy form, since it gives a monoquinoxaline with *o*-phenylenediamine (431), as does rhodizonic acid (432). On the other hand, when oxidised, croconic acid yields leuconic acid



(431)



(432)

which, despite its four molecules of water of crystallisation, is represented by the structure (430). It gives the double derivative (433) with toluylene diamine, which still has one keto group free to react with hydroxylamine, giving the oxime. Homolka[4] has also shown that leuconic acid breaks down on hydrolysis with warm sodium carbonate solution to sodium mesoxalate and glyoxal, a further confirmation of its structure (434).

Leuconic acid, in the form of its tetrahydrate is colourless, and gives colourless derivatives. It forms a yellow penta-oxime with hydroxylamine which explodes at 172° ; reduction of this oxime yields penta-amino *cyclo*pentadiene.

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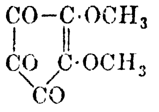
[1] Maquenne, *Ann. Chim.*, 1887, **12**, 112.

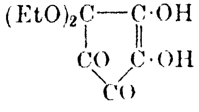
[2] Homolka, G.P. 268, 741 and 370, 322.

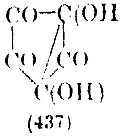
[3] Will, *Ann.*, 1861, **118**, 187.

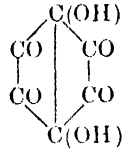
[4] Homolka, *Ber.*, 1922, **55B**, 1310.

Croconic acid forms golden yellow leaflets with $3H_2O$. It is a dibasic acid and yields a red crystalline anhydride, which yields red salts. With ammonia it gives a tri-imide of leuconic acid, and with hydroxylamine the penta-oxime of the same acid. It is best prepared from diaminotetrahydroxybenzene by warming it with four times its weight of potassium carbonate dissolved in sixty parts of water, carrying two parts of freshly precipitated manganese dioxide in suspension.[1] On filtering, acidifying and adding barium chloride, the barium salt is obtained. Barium croconate forms golden yellow plates. The acid has been exhaustively investigated by Malakovski and Prevendovski,[2] who were able to prepare its dimethyl (435) and diethyl esters, and who also


(435)


(436)


(437)



obtained an 'acetal' having the formula (436). Carpéni[3] favours a bridge structure for croconic and rhodizonic acids (437), on the basis of spectrographic and electrometric determinations, but the view is not generally accepted.

ACID HALIDES, ANHYDRIDES AND AMIDES

Benzoyl chloride appears to have been the earliest acid halide to be prepared, Liebig and Wöhler having obtained it in 1832[4] by the action of dry chlorine on pure benzaldehyde. This method is general for the preparation of numerous acid chlorides, and involves the chlorination of the aldehyde group ;

$$R\,.\,CHO + Cl_2 \longrightarrow RCO\,.\,Cl + HCl$$

the reaction is only successful with aromatic aldehydes, and in the absence of water.

Acetyl chloride was next discovered by Gerhardt in 1853[5] by the action of phosphorus oxychloride on fused potassium acetate, and since this time the acid chlorides, and in some cases, fluorides, bromides and iodides have been prepared for the vast majority of acids.

In general, the acid chlorides are produced directly from the acid ; and the following reagents are available, phosphorus tri- and pentachlorides, phosphorus oxychloride, phosgene, thionyl and sulphuryl chlorides and benzenesulphonyl chloride. In nearly every case thionyl chloride offers a ready method of obtaining the acid chloride free from impurities. If the acid be mixed with thionyl chloride and warmed the reaction is as follows :—

$$R\,.\,COOH + SOCl_2 \longrightarrow SO_2 + HCl + R\,.\,COCl$$

in which it will be noted the products of decomposition of thionyl chloride are both gaseous. Excess of thionyl chloride is usually employed, the surplus being removed by distillation, or in the case of acid chlorides which are easily decomposed by heat, the excess may be destroyed with anhydrous formic acid :—

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[1] Nietzski and Benckiser, *Ber.*, 1875, **18**, 509.

[2] Malakovski and Prevendovski, *ibid.*, 1938, **71B**, 2241.

[3] Carpéni, *C.R.*, 1938, **206**, 432, 601.

[4] Liebig and Wöhler, *Ann.*, 1832, **3**, 262.

[5] Gerhardt, *Ann. Chim. Phys.*, 1853, **3**, **37**, 285.

$$HCOOH + SOCl_2 \longrightarrow CO + SO_2 + 2HCl.$$

The residual crude acid chloride may usually be purified by distillation in vacuum. The use of phosphorus pentachloride is occasionally convenient, but for large quantities is expensive ; the reaction proceeds :—

$$PCl_5 + R.COOH \longrightarrow R.COCl + HCl + POCl_3$$

and it is frequently found difficult to separate the acid chloride from the phosphorus oxychloride. Frequently, too, phosphorus pentachloride acts as a chlorinating agent ; its action upon acetic acid ultimately yields trichloroacetyl chloride, whilst at 200° it converts benzoic acid to benzotrichloride. On the other hand, phosphorus trichloride, although demanding a higher temperature for its use, is more economical, each mole converting three moles of acid to the chloride :—

$$3R.COOH + PCl_3 \longrightarrow H_3PO_4 + 3R.COCl.$$

The disadvantage lies in the tendency of part of the phosphorus chloride to be reduced, forming traces of phosphines and phosphine chlorides which contaminate the product.

Phosgene is useful for preparing the acid chlorides of the simpler aliphatic acids ; reacting with the sodium salts under pressure :—

$$R.COONa + COCl_2 \longrightarrow R.COCl + NaCl + CO_2.$$

It is also possible to obtain excellent yields of the simpler acid chlorides by allowing phosgene to react with the acid anhydride under pressure, e.g.,

$$(CH_3CO)_2O + COCl_2 \longrightarrow 2CH_3COCl + CO_2.$$

Methods which may ultimately assume considerable importance are those in which an alkyl halide is heated with carbon monoxide under pressure, in the presence of a copper catalyst. The reaction

$$R.Cl + CO \longrightarrow R.COCl$$

takes place.

The oxidation of certain chlorinated derivatives of ethylene by the oxygen of air, in the presence of catalysts, constitutes a group of methods of considerable industrial importance. Those commonly met with are :—

$$\begin{aligned}
CHCl{=}CHCl + O &\longrightarrow CH_2Cl.COCl\\
CHCl_2{=}CHCl + O &\longrightarrow CHCl_2.COCl\\
CCl_2{=}CCl_2 + O &\longrightarrow CCl_3.COCl
\end{aligned}$$

Another reaction of importance is the interaction of phosgene and ethylene to give β-chloropropionyl chloride.

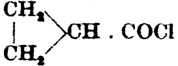
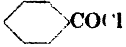
Acid fluorides are obtainable ; in the aromatic series they are obtainable by heating the acid chloride with potassium acid fluoride. Benzoyl fluoride was obtained as far back as 1863 by Borodin by this process. Aliphatic fluorides may be obtained by carrying out the reaction in the presence of benzoyl chloride, or by using benzoyl fluoride direct :

$$\begin{aligned}
C_6H_5.COCl + HFKF &\longrightarrow C_6H_5.COF\\
C_6H_5.COF + R.COOH &\longrightarrow C_6H_5.COOH + R.COF
\end{aligned}$$

The success of the method depends on the aliphatic acyl fluoride having a boiling point lower than that of benzoyl fluoride, 162°. Acids and their chlorides also react with zinc fluoride to give the acyl fluoride.

Acyl bromides are almost exclusively obtained by the use of phosphorus tribromide—or by its equivalent, the simultaneous use of red phosphorus and

TABLE XLIII—SOME ACID CHLORIDES AND BROMIDES

Acid halide	Formula	Chloride			Bromide		
		M.P.	B.P.	Density	M.P.	B.P.	Density
Acetyl	$CH_3 . COCl$	− 112°	51°	$1{\cdot}1051^{20}_{4}$	− 96°	81°	1·52
Chloroacetyl	$CH_2Cl . COCl$	—	106°	—	—	133–135°	1·913
Dichloroacetyl	$CHCl_2 . COCl$	—	105–107°	—	—	—	—
Trichloroacetyl	$CCl_3 . COCl$	—	118°	$1{\cdot}629^{16}$	—	—	—
Bromoacetyl	$CH_2Br . COCl$	—	127°	1·908	—	149–150°	$2{\cdot}317^{21}_{21}$
Dibromoacetyl	$CHBr_2 . COCl$	—	—	—	—	194°	—
Tribromoacetyl	$CBr_3 . COCl$	—	—	—	121–122°	—	—
Iodoacetyl	$CH_2I . COCl$	—	49–52°/15 mm.	2·25	—	—	—
Difluoroacetyl	$CF_2H . COCl$	—	25°	—	—	—	—
Propionyl	$C_2H_5 . COCl$	—	77–78°	$1{\cdot}0646^{20}_{4}$	—	103–104°	1·521
***n*-Butyryl**	$C_3H_7 . COCl$	—	101–102°	$1{\cdot}028^{20}$	—	23–25°/10 mm.	$1{\cdot}416^{16}_{4}$
***n*-Valeryl**	$C_4H_9 . COCl$	—	127–128°	$1{\cdot}015^{15}$	—	64°/66 mm.	—
***n*-Capronyl**	$C_5H_{11} . COCl$	—	152°	—	—	175–176°	—
***n*-Heptoyl**	$C_6H_{13} . COCl$	—	77°/23 mm.	$0{\cdot}967^{15}$	—	—	—
***n*-Caprylyl**	$C_7H_{15} . COCl$	—	83°/15 mm.	$0{\cdot}973^{8}$	—	—	—
***n*-Pelargonyl**	$C_8H_{17} . COCl$	− 60°	98°/13 mm.	$0{\cdot}959^{0}$	—	—	—
***n*-Capryl**	$C_9H_{19} . COCl$	—	114°/15 mm.	—	—	—	—
***n*-Undecylyl**	$C_{10}H_{21} . COCl$	—					
Lauryl	$C_{11}H_{23} . COCl$	− 17°	135–140°/10 mm.	—			
Myristyl	$C_{13}H_{27} . COCl$	—	174°/16 mm.	—			
Palmityl	$C_{15}H_{29} . COCl$	—	194–195°/17 mm.	—			
Stearyl	$C_{17}H_{33} . COCl$	—	203°	—			
***iso*-Butyryl**	$(CH_3)_2CH . COCl$	—	92°	$1{\cdot}0174^{20}_{4}$	—	116°	—
***iso*-Valeryl**	$(CH_3)_2CHCH_2 . COCl$	—	113–114°	$0{\cdot}9887^{20}_{4}$	—	143°	—
Trimethylacetyl	$(CH_3)_3C . COCl$	—	105–106°	—			
***α, β*-Dimethylbutyryl**	$(CH_3)_2CH . CH(CH_3)COCl$	—	136–137°	0·9961			
***ter*-Butylacetyl**	$(CH_3)_3C . CH_2 . COCl$		130°	$0{\cdot}9872^{22}_{4}$			
Acrylyl	$CH_2{=}CH . COCl$	—	75°	1·14			
Trichloroacrylyl	$CCl_2{=}CCl . COCl$	—	158°	1·597			
Crotonyl	$CH_2{=}CH . CH_2 . COCl$	—	124–126°	$1{\cdot}0822^{17}$			
Hexenoic	$CH_2{=}CH(CH_2)_3 . COCl$	—	59–60°/24 mm.	—			
Oleyl	$CH_3(CH_2)_7CH{=}CH(CH_2)_7 . COCl$	—	213°/13 mm.	—			
***Cyclo*propylcarboxylic**	 $\begin{matrix} CH_2 \\ \vert \\ CH_2 \end{matrix} \!\! > CH . COCl$	—	120–122°	—			
1-*Cyclo*hexanecarboxylic			86°/11 mm.	—			

Cyclohexylideneacetic	$C_6H_{10}{=}CH . COCl$	—	123°/28 mm.	—			
Benzoyl	$C_6H_5 . COCl$	− 1°	197°	$1{\cdot}21^{20}$	—	217–218°	—
***o*-Fluorobenzoyl**	$C_6H_4F . COCl(1, 2)$	—	99°/13 mm.	—			
***m*-Fluorobenzoyl**	$C_6H_4F . COCl(1, 3)$	—	91°/18 mm.	—			
***p*-Fluorobenzoyl**	$C_6H_4F . COCl(1, 4)$	—	104°/38 mm.	—			
***o*-Chlorobenzoyl**	$Cl . C_6H_4 . COCl(1, 2)$	—	93–95°/10 mm.				
***m*-Chlorobenzoyl**	$ClC_6H_4 . COCl(1, 3)$	—	222°	—			
***p*-Chlorobenzoyl**	$ClC_6H_4 . COCl(1, 4)$	16°	111°/18 mm.	—			
2, 3-Dichlorobenzoyl	$Cl_2C_6H_3 . COCl(2, 3, 1)$	—	140° 14 mm.	—			
2, 4-Dichlorobenzoyl	$Cl_2C_6H_3 . COCl(2, 4, 1)$	—	150°/30 mm.	—			
2, 5-Dichlorobenzoyl	$Cl_2C_6H_3 . COCl(2, 5, 1)$	—	137°/15 mm.	—			
2, 6-Dichlorobenzoyl	$Cl_2C_6H_3 . COCl(2, 6, 1)$	—	142°/11 mm.	—			
3, 5-Dichlorobenzoyl	$Cl_2C_6H_3 . COCl(3, 5, 1)$	—	135°/27 mm.	—			
***o*-Bromobenzoyl**	$Br . C_6H_4 . COCl(1, 2)$	—	116°/11 mm.	—			
***m*-Bromobenzoyl**	$Br . C_6H_4 . COCl(1, 3)$	—	240°	—			
***p*-Bromobenzoyl**	$Br . C_6H_4 . COCl(1, 4)$	42°	136°/20 mm.	—			
***o*-Iodobenzoyl**	$I . C_6H_4 . COCl(1, 2)$	35–40°	—	—			
***m*-Iodobenzoyl**	$I . C_6H_4 . COCl(1, 3)$	—	159°/23 mm.	—			
***p*-Iodobenzoyl**	$I . C_6H_4 . COCl(1, 4)$	71°	—	—			
***o*-Toluyl**	$CH_3 . C_6H_4 . COCl(1, 2)$	—	110°/29 mm.	—			
***m*-Toluyl**	$CH_3 . C_6H_4 . COCl(1, 3)$	—	109°/15 mm.	—			
***p*-Toluyl**	$CH_3 . C_6H_4 . COCl(1, 4)$	—	95°/10 mm.	—			
***o*-Ethylbenzoyl**	$C_2H_5 . C_6H_4 . COCl(1, 2)$	—	219°	—			
***o*-Propylbenzoyl**	$C_3H_7 . C_6H_4 . COCl(1, 2)$	—	236°	—			
***p*-*iso*-Propylbenzoyl** (cuminyl)	$C_3H_7 . C_6H_4 . COCl(1, 4)$	—	256–258°	—			
Phenylacetyl	$C_6H_5CH_2 . COCl$	—	104–105°/22 mm.				
Phenyl propiolyl	$C_6H_5CH_2 . CH_2 . COCl$	—	115°/12 mm.	—			
Cinnamoyl	$C_6H_5 . CH{=}CH . COCl$	—	122–123°/8 mm.	—			
Phenylproprolyl	$C_6H_5 . C{\equiv}C . COCl$	—	119°/12 mm.	—			
Diphenylacetyl	$(C_6H_5)_2 . CH . COCl$	56°	—	—			
Triphenylacetyl	$(C_6H_5)_3 . C . COCl$	128–129°	—	—			
Oxalyl	$(COCl)_2$	− 12°	64°	1·484			
Malonyl	$CH_2(COCl)_2$	− 13°	47°/15 mm.	1·448			
Succinyl	$(CH_2)_2(COCl)_2$	20°	87–88°/18 mm.	1·36			
Glutaryl	$(CH_2)_3(COCl)_2$	—	216–218°	—			
Adipyl	$(CH_2)_4(COCl)_2$	—	126°/14 mm.	—			
Pimelyl	$(CH_2)_5(COCl)_2$	—	137°/15 mm.	—			
Suberyl	$(CH_2)_6(COCl)_2$	—	147°/12 mm.	—			
Azelayl	$(CH_2)_7(COCl)_2$	—	166°/18 mm.	—			
Sebacyl	$(CH_2)_8(COCl)_2$	—	170°/16 mm.	—			
Fumaryl	$ClCO . CH{=}CH . COCl$	—	60°/10 mm.	—			

bromine. Double decomposition, particularly with oxalyl bromide, is also a satisfactory way of obtaining volatile acid bromides. The aerial oxidation, in the presence of catalysts of the bromo-ethylenes :—

$$CHBr{=\!=}CHBr \xrightarrow{+\,O} CH_2BrCOBr$$

$$CBr_2{=\!=}CHBr \xrightarrow{+\,O} CHBr_2COBr$$

$$CBr_2{=\!=}CBr_2 \xrightarrow{+\,O} CBr_3COBr$$

proceeds even more satisfactorily than with the corresponding chlorine compounds ; unfortunately, the bromo-ethylenes are not readily available.

Most acid iodides are obtained by double decomposition, using an acid chloride and calcium iodide.

In Table XLIII and Table XLIV the salient physical properties of a number of common acid halides are shown. The reactions of acid halides are, on the whole, fairly simple ; the tendency is for the halogen atom to combine with hydrogen, and for the two remaining residues to unite ; in this way the acid itself is regenerated with water ; esters are formed with alcohols, and a large variety of acyl compounds obtained, as exemplified below :—

TABLE XLIV

SOME ACYL FLUORIDES AND IODIDES

Acid halide	Formula	Fluoride		Iodide	
		M.P.	B.P.	M.P.	B.P.
Formyl	$H\,.\,COX$	—	—26°	—	—
Acetyl	$CH_3\,.\,COX$	—	20·8°	—	108°
Propionyl	$C_2H_5\,.\,COX$	—	44°	—	128°
Butyryl	$C_3H)_7\,.\,COX$	—	67°	—	148°
Isobutyryl	$(CH_3)_2CH\,.\,COX$	—	57°	—	168°
Dichloroacetyl	$CHCl_2\,.\,COX$	—	71°	—	—
Benzoyl	$C_6H_5\,.\,COX$	—	162°	3°	117°/14 mm.

$R\,.\,CO\,.\,Cl + H_2O$ —— $R\,.\,COOH$ acid
$R\,.\,CO\,.\,Cl + HO\,.\,R^1$ —— $R\,.\,COOR^1$ ester
$R\,.\,CO\,.\,Cl + NH_3$ —— $R\,.\,CONH_2$ amide
$R\,.\,CO\,.\,Cl + NH_2C_6H_5$ —— $R\,.\,CONHC_6H_5$ anilide
$R\,.\,CO\,.\,Cl + NH_2NH_2$ —— $R\,.\,CONH\,.\,NH_2$ hydrazide
$R\,.\,CO\,.\,Cl + NaN_3$ —— $R\,.\,CO\,.\,N_3$ azide
$R\,.\,CO\,.\,Cl + AgCN$ —— $R\,.\,CO\,.\,CN$ acyl cyanide
$R\,.\,CO\,.\,Cl + AgNCO$ —— $R\,.\,CO\,.\,NCO$ acyl isocyanate

The use of acyl chlorides in the Friedel Crafts reaction has already been discussed (p. 216).

ACID ANHYDRIDES

Williamson[1] in 1850 predicted that there should exist an 'anhydride' of acids such as acetic, but it remained for Gerhardt[2] in 1852 actually to prepare the substance ; which he accomplished by the action of acetyl chloride upon anhydrous sodium acetate

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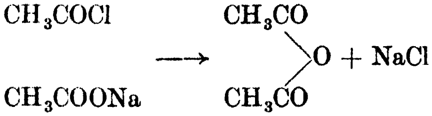
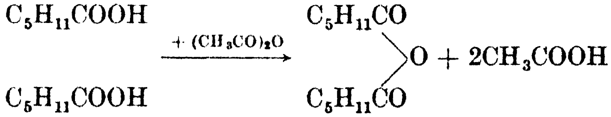
[1] Williamson, *Ann. Chim. Phys.*, 1850, **28**, 241.
[2] Gerhardt, *C.R.*, 1852, **34**, 755.



$$\begin{matrix} CH_3COCl \\ CH_3COONa \end{matrix} \longrightarrow \begin{matrix} CH_3CO \\ CH_3CO \end{matrix}\!\!>\!O + NaCl$$

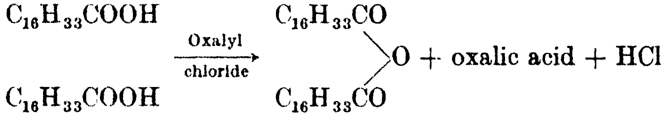
The reaction has been used considerably for the preparation of this substance. The direct dehydration of aliphatic acids, even by such reagents as phosphorus pentoxide is difficult to bring about with any consistent yield of acid anhydride ; even with acetic acid resinification sets in and the yield is only about 30 per cent. of the theoretical, whilst with higher acids resinification is almost complete. Fortunately, nearly all the higher acid anhydrides can be prepared from acetic anhydride and the acid in question. Thus, caproic anhydride is obtained by heating caproic acid with an excess of acetic anhydride.



$$\begin{matrix} C_5H_{11}COOH \\ C_5H_{11}COOH \end{matrix} \xrightarrow{+\,(CH_3CO)_2O} \begin{matrix} C_5H_{11}CO \\ C_5H_{11}CO \end{matrix}\!\!>\!O + 2CH_3COOH$$

If a good excess of acetic anhydride is used the acetic acid formed can be distilled off with it leaving the crude caproic anhydride to be purified by fractionation in vacuum.

Another exceptionally useful reagent for the preparation of the higher aliphatic acid chlorides is oxalyl chloride ; heated with even long-chain acids, e.g. Margaric acid, the anhydride is formed and may be distilled *in vacuo* from

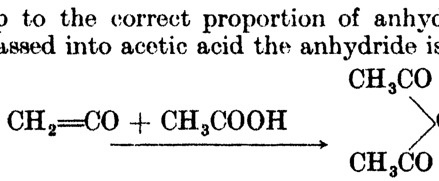


$$\begin{matrix} C_{16}H_{33}COOH \\ C_{16}H_{33}COOH \end{matrix} \xrightarrow[\text{chloride}]{\text{Oxalyl}} \begin{matrix} C_{16}H_{33}CO \\ C_{16}H_{33}CO \end{matrix}\!\!>\!O + \text{oxalic acid} + HCl$$

the anhydrous oxalic acid. Yields up to 70 per cent. in the aliphatic series can be obtained by this reaction ; in the aromatic series the yields are quantitative. A variant of the method is to use the acid chloride and anhydrous oxalic acid. Industrially, acetic anhydride can be made by the action of a regulated amount of phosgene on sodium acetate :—

$$2CH_3COONa + COCl_2 \longrightarrow (CH_3CO)_2O + 2NaCl$$

Since, however, much of the acetic anhydride used in industry is in admixture with acetic acid for the acetylation of cellulose in making rayon, and since during the acetylation the excess of acetic acid is not destroyed, but merely requires bringing up to the correct proportion of anhydride, keten is widely used. If keten is passed into acetic acid the anhydride is formed :—



$$CH_2{=}CO + CH_3COOH \longrightarrow \begin{matrix} CH_3CO \\ CH_3CO \end{matrix}\!\!>\!O$$

This reaction can be used also for making the pure anhydride, but is particularly adapted to ' topping up ' acetylation mixtures.

Some unusual methods of making acetic anhydride include Broughton's method in which carbon bisulphide and lead acetate are heated [1] together :—

$$2(CH_3\,.\,COO)Pb + CS_2 \longrightarrow 2(CH_3CO)O + CO_2 + 2PbS$$

and the procedure due to Lachowitz [2] in which two moles of acid chloride are warmed with one of dry silver oxide

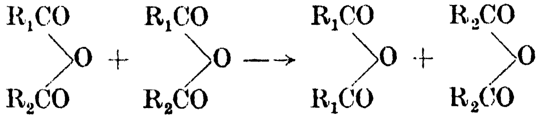
$$2R\,.\,COCl + Ag_2O \longrightarrow (R\,.\,CO)_2O + 2AgCl$$

---

[1] Broughton, *J.C.S.*, 1865, **18**, 21.

[2] Lachowitz, *Ber.*, 1884, **17**, 1283.

Mixed acid anhydrides can be made, but are very unstable, and on distillation revert to a mixture of the two corresponding symmetrical anhydrides :—



$$\begin{array}{c}R_1CO\\ \quad\rangle O\\ R_2CO\end{array} + \begin{array}{c}R_1CO\\ \quad\rangle O\\ R_2CO\end{array} \longrightarrow \begin{array}{c}R_1CO\\ \quad\rangle O\\ R_1CO\end{array} + \begin{array}{c}R_2CO\\ \quad\rangle O\\ R_2CO\end{array}$$

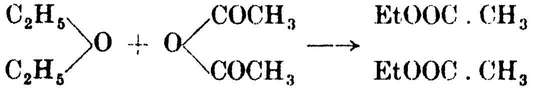
They may be obtained by suitable variants of the methods already described—such as the action of the acid chloride of one acid on the sodium salt of another, or the action of keten on an acid other than acetic acid. An exception to the rule of mixed anhydride instability is acetoformic anhydride, H.CO.O.$COCH_3$[1] which distils undecomposed.

Application of the reactions of acid anhydrides is directed primarily to the process of acylation in which acids or amino bodies are converted to esters or amides, e.g.,

$$R.OH + (CH_3CO)_2O = R.O.COCH_3 + CH_3COOH$$
$$R.NH_2 + (CH_3CO)_2O = R.NHCOCH_3 + CH_3COOH$$

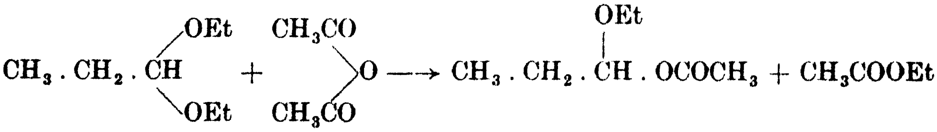
In the acetylation of glycols and glycerols with acetic anhydride care must be taken to see that the reactants are not fed into the apparatus faster than they can react ; serious explosions have taken place during the acetylation of glycol owing to neglect of this precaution.

The use of acid anhydrides in the Friedel-Crafts reaction has already been discussed ; it is to be noted, however, that acid anhydrides have one or two reactions which are peculiar to the group. Their reaction with ethers in the presence of a catalyst (such as HBr, $SnCl_4$, $FeCl_3$, etc.) is to break them down with the formation of esters, e.g.,



$$\begin{array}{c}C_2H_5\\ \quad\rangle O\\ C_2H_5\end{array} + O\!\begin{array}{l}\diagup COCH_3\\ \diagdown COCH_3\end{array} \longrightarrow \begin{array}{c}EtOOC.CH_3\\ EtOOC.CH_3\end{array}$$

a reaction which is occasionally of value in characterising ethers. Acetals behave similarly, but, of course, two esters are obtained :—



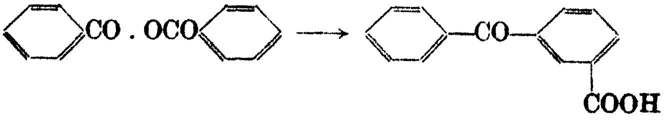
$$CH_3.CH_2.CH\!\begin{array}{l}\diagup OEt\\ \diagdown OEt\end{array} + \begin{array}{c}CH_3CO\\ \quad\rangle O\\ CH_3CO\end{array} \longrightarrow CH_3.CH_2.\overset{\displaystyle OEt}{\overset{|}{C}}H.OCOCH_3 + CH_3COOEt$$

When passed over a reduced cadmium catalyst, acid anhydrides are converted almost quantitatively to the corresponding ketone.

$$(CH_3CO)_2O \xrightarrow{Cd} CH_3.CO.CH_3 + CO_2$$

The aromatic acid anhydrides are often best prepared by the action of quinoline or pyridine on the acid chloride, followed by the addition of water.

The action of heat on benzoic anhydride leads to benzophenone and anthraquinone, but the action of zinc chloride leads to the substantial production of benzophenone-3-carboxylic acid :—



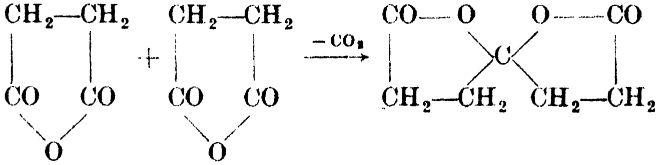
a reaction which has the appearance of a meta-migration.[2]

[1] Behal, *Ann. Chim.*, 1900, [7] **20**, 419.

[2] Dobner, *Ann.*, 1881, **210**, 278.

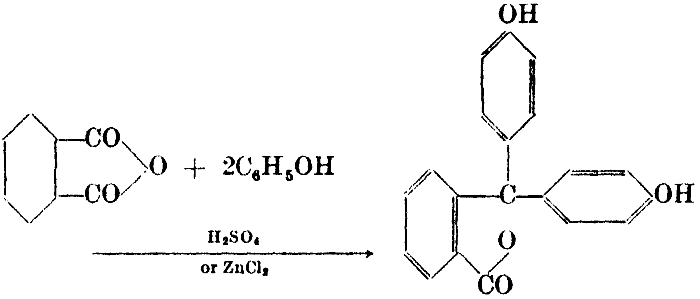
Certain dibasic acids form cyclic anhydrides with great ease, e.g., succinic and glutaric acid—a reaction which may be expected on stereochemical grounds ; the ability to form such cyclic anhydrides is seen at its best in the benzene-*o*-dicarboxylic acid series, phthalic anhydride being more easily prepared than the acid.

Succinic anhydride when heated for several hours at its boiling point passes into a *spiro* compound—a double lactone of acetone diacetic acid :—



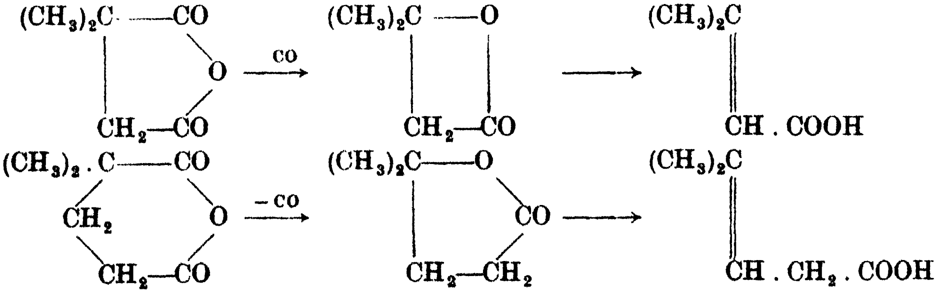
In addition, succinic, glutaric and phthalic anhydrides unite in showing unusual stability of the ring, being able to condense by loss of oxygen from one —CO group with the formation of a group of substances of unusual properties and importance.

Thus, both succinic and phthalic anhydrides condense readily with phenols, and the reaction is capable of being carried out with highly substituted phenols and phthalic anhydrides. The reaction is typified by the formation of phenolphthalein.



Both succinic and glutaric anhydrides give compounds of the same type and the range has been widely investigated. The coloured derivatives of this group have afforded a very valuable range of indicators ; a full discussion of their structure is reserved to Chapter XV of Vol. II.

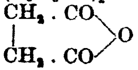
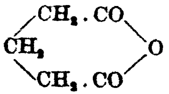
Unusual properties are also associated with substituted anhydrides of the succinic and glutaric anhydride series in which the carbon adjacent to one of the carbonyl groups is quaternary. Treated with anhydrous aluminium chloride in chloroform they are converted first to the lactone of a hydroxy acid and then to an unsaturated acid :—

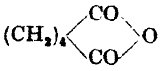
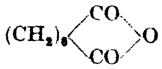
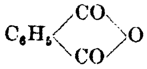
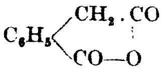
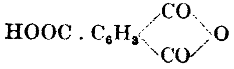
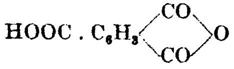
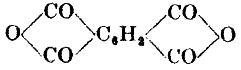
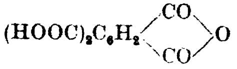
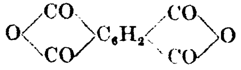
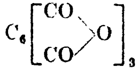
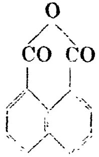


A well-known instance of this rearrangement, in which carbon monoxide is evolved, is that of the conversion of camphoric anhydride to *iso*laurolonic (β-campholytic acid).

TABLE XLV

SOME ACID ANHYDRIDES

Acid from which the anhydride is derived	Formula	Properties
Acetic and formic	$HCO \cdot O \cdot COCH_3$	b. 30°. Stable
Acetic	$(CH_3CO)_2O$	m. − 73° ; b. 139·5°. d = 1.082^{20}
Propionic	$(C_2H_5CO)_2O$	b. 72°/11 mm. b. 168°/760 mm.
Butyric	$(C_3H_7CO)_2O$	b. 198°. d = 0·978^{15}
Valeric	$(C_4H_9CO)_2O$	b. 110/15 mm. d = 0·922^{17}
Caproic	$(C_5H_{11}CO)_2O$	b. 241–243°
Oenanthic	$(C_6H_{13}CO)_2O$	b. 258°. b. 164°/35 mm. d = 0·9217^{17}
Caprylic	$(C_7H_{15}CO)_2O$	m. 1° ; b. 280–285°. d = 0·965^{70}
Pelargonic	$(C_8H_{17}CO)_2O$	m. 16° ; b. 207°/15 mm.
Capric	$(C_9H_{19}CO)_2O$	m. 24° ; d = 0·867^{0}
Lauric	$(C_{11}H_{23}CO)_2O$	m. 42° ; d = 0·555^{70}
Myristic	$(C_{13}H_{27}CO)_2O$	m. 53–54° ; d = 0·8502^{70}
Palmitic	$(C_{15}H_{31}CO)_2O$	m. 63–64° ; d = 0·847^{70}
Stearic	$(C_{17}H_{35}CO)_2O$	m. 71–72° ; d = 0·844^{70}
iso-Butyric	$[(CH_3)_2CH \cdot CO]_2O$	b. 73°/18 mm. d = 0·978^{16}
iso-Valeric	$[(CH_3)_2CH \cdot CH_2CO]_2O$	b. 102–103°/15 mm. b. 215°/760. d = 0·929^{27}
Trimethylacetic	$[(CH_3)_3CCO]_2O$	b. 190°
Acrylic	$(CH_2{=}CHCO)_2O$	b. 97°/35 mm. d = 1·094°
Trifluoroacetic	$(CF_3CO)_2O$	m. − 65° ; b. 40°
Monochloroacetic	$(CH_2Cl \cdot CO)_2O$	
Dichloroacetic	$(CHCl_2CO)_2O$	b. 140°/35 mm. d = 1·574^{31}
Monobromoacetic	$(CH_2BrCO)_2O$	m. 42° ; b. 133–135°/12·5 mm.
Monoiodoacetic	$(CH_2ICO)_2O$	m. 46°
Oleic	$[CH_3(CH_2)_7CH{=}CH(CH_2)_7CO]_2O$	m. 22–24°
Docosen-9, oic	$[CH_3(CH_2)_{11}CH{=}CH(CH_2)_7CO]_2O$	m. 46·5°
Benzoic	$(C_6H_5CO)_2O$	m. 42°
Succinic		m. 119·6° ; b. 261°
Chlorosuccinic		rac. m. 40–41° ; dextro. m. 80°
Bromosuccinic		rac. m. 30–31°
Glutaric		m. 56–57° ; b. 286–288°

Adipic		m. 22°
Pimelic		m. 55°
Suberic anyhdride		m. 66°
Phthalic		m. 128°; b. 248·5° sublimes
Homophthalic		m. 141°
Hemimellic	 (1, 2, 3)	m. 193–196°
Trimellitic	 (1, 2, 4)	m. 163–165°; b. 240–245°/14 mm
Mellophanic	 (1, 2, 3, 4)	m. 193–196°
Prehnitic	 (3, 5, 1, 2)	m. 239°
Pyromellitic	 (1, 2, 4, 5)	m. 286°
Mellitic		m. ca. 300°
Naphthalic		m. 274°

Esters

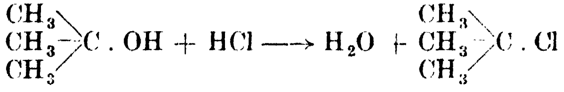
This section deals only with the formation and general properties of esters, some of which are shown in Table XLVI. The reactions of ketonic an ddibasic esters which depend for their success on the active methylene group are specially considered in Appendix III of this chapter.

Esters have been known since the middle of the eighteenth century when Lauraquais prepared ethyl acetate by heating strong acetic acid with alcohol. Scheele prepared ethyl benzoate in 1785, but was inclined to deny that ethyl acetate could be obtained from the acid and spirit alone; he observed that a small trace of mineral acid was necessary. The use of this small amount of acid is necessary to stimulate the process of esterification, although (as proved originally by Pelletier in 1786) the ester is slowly formed from the acid in the complete absence of catalysts. It was soon realised that the reaction

$$C_2H_5OH + HOOC\,.\,CH_3 \rightleftharpoons H_2O + C_2H_5O\,.\,COCH_3$$

and similar reactions, are reversible or 'balanced' in the sense that the four substances, acid, alcohol, ester and water come to an equilibrium. In some cases it is only possible to drive this equilibrium to the ester side by the use of an agent to remove the water; in other cases, the equilibrium is so far on to the ester side that a catalyst is only necessary to accelerate the combination. In the former case a considerable body of sulphuric or phosphoric acid is required; in the latter it is sufficient to dissolve some hydrogen chloride in the alcohol.

Speed of esterification decreases when the hydroxyl to be acylated is attached to a secondary or tertiary carbon atom; an exception to this is the almost complete conversion of *ter*-butanol to *ter*-butyl chloride by shaking for a few moments with concentrated hydrochloric acid



$$\left.\begin{array}{l}CH_3\\CH_3\\CH_3\end{array}\right>C\,.\,OH + HCl \longrightarrow H_2O + \left.\begin{array}{l}CH_3\\CH_3\\CH_3\end{array}\right>C\,.\,Cl$$

Methods of Ester Preparation

(1) The treatment of an alcohol and acid with an auxiliary mineral acid.

(*a*) *Sulphuric Acid.*—This method is mainly used for preparing simple esters such as ethyl acetate, in small quantities for laboratory purposes.

(*b*) *Hydrochloric Acid.*—The use of this was initiated by Fischer and Speier[1]; the alcohol is often saturated with hydrogen chloride, then heated under reflux with the acid. It is particularly useful for aromatic acids, e.g., benzoic or cinnamic.

(2) The use of the acid and alcohol alone.

(*a*) *Without Devices to remove Water.*—In the case of comparatively strong acids, such as oxalic and chloroacetic acids, the esters of simple alcohols may be obtained by simple interaction of the two reactants in a completely anhydrous state. Dimethyl oxalate is obtained in this way. In the case of some dibasic acids, e.g., tartaric, refluxing with ethyl alcohol will only esterify one carboxyl group, thus giving a very convenient method of preparing the half esters for synthetic purposes.

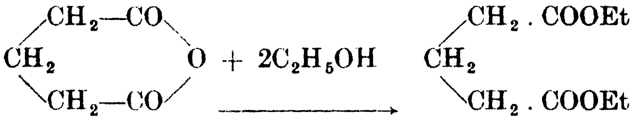
(*b*) *With removal of Water.*—If, however, tartaric acid and absolute alcohol are heated together with benzene, in a flask with a Dean and

---

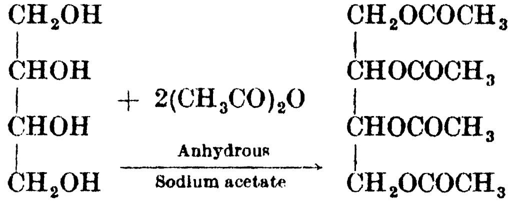
[1] Fischer and Speier, *Ber.*, 1895, **28**, 3252.

Stark condenser and return, the water can be distilled off and only the benzene and alcohol returned to the flask, thus effecting a continual removal of water; in such cases, esterification proceeds to the neutral ester.

(3) Alcohols and phenols may be converted to the esters by the use of acid chlorides or anhydrides, e.g.,



Glutaric anhydride → Diethyl glutarate

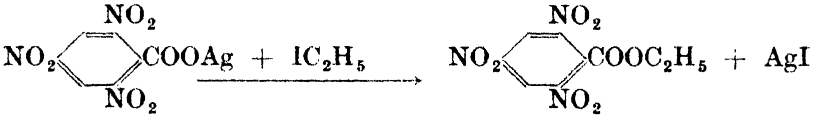


$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + 2(CH_3CO)_2O \xrightarrow[\text{Sodium acetate}]{\text{Anhydrous}} \begin{array}{l} CH_2OCOCH_3 \\ | \\ CHOCOCH_3 \\ | \\ CHOCOCH_3 \\ | \\ CH_2OCOCH_3 \end{array}$$

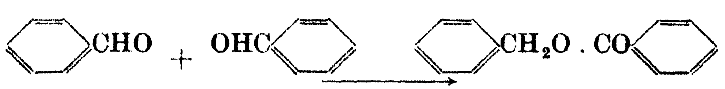
Erythritol → Erythritol tetraacetate

(4) The use of an aryl acid chloride, e.g., benzoyl, *p*-nitrobenzoyl or 3, 5-dinitrobenzoyl chloride affords a good method of preparing identification compounds from small quantities of alcohols or phenols. The alcohol or phenol is suspended or dissolved in a little cold dilute caustic soda solution and shaken with a few drops or crystals of the acid chloride. The ester separates and may be crystallised for identification. This is often called the Schotten-Baumann reaction.

(5) In some cases where esterification is precluded by ordinary methods, as in the case of the 2, 6 disubstituted benzoic acids—especially those with halogen or nitro groups—it is possible to make the ester by refluxing the silver salt of the acid with an alkyl iodide, e.g., with trinitrobenzoic acid :—



(6) In some cases, mainly aromatic, aldehydes can be induced to form esters by a reaction, the net result of which is



(Tischtschenko's reaction)[1]

This method is used industrially to prepare benzyl benzoate, but the use of aluminium ethoxide, or of a trace of sodium benzyl oxide, is necessary to start the reaction.

(7) The interaction of acids (formic excepted) with ethylene is a reaction capable of giving an excellent yield of ester :—

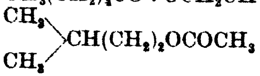
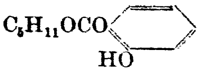
$$CH_2{=}CH_2 + CH_3COOH \longrightarrow CH_3 . COOEt$$

---

[1] Tischtschenko, *Ch. Ztg.*, 1930, **11**, 196.

TABLE XLVI

SOME ODOROUS ESTERS

Ester	Formula	B.P.	Comment
Allyl caproate	$CH_3(CH_2)_4CO . OCH_2CH{=}CH_2$	—	Strong pineapple flavour.
Amyl acetate	 $(CH_3)_2CH(CH_2)_2OCOCH_3$	*n*-149° *iso*-142°	A ' pear ' flavoured substance.
Amyl benzoate	$C_5H_{11}O . COC_6H_5$	*n*-261°	Has an odour reminiscent of amber and is used as a fixative in perfume blending.
Amyl butyrate	$C_5H_{11}O . COC_3H_7$	*iso*-178°	A so-called ' pineapple ' type, largely superseded by allyl caproate. A ' touch ' is used in apricot flavours.
Amyl heptoate	$C_5H_{11}O . COC_6H_{13}$	—	Has a strong fruity odour; mainly used in small quantities to introduce ' freshness ' to perfumes.
iso-Amyl salicylate		277°; 152°/15 mm.	A heavy clover flower odour; used in orchid, trefoil and Californian poppy perfumes.
Amyl *iso*valerate	$C_5H_{11}OCOC_4H_9$	*iso*-194°	Has a sharp apple-smell.
Benzyl acetate	$C_6H_5CH_2O . COCH_3$	216°	Has been isolated from the essential oils of jasmine, neroli and ylang-ylang. Used as the basis of the cheap imitations of jasmine.
Benzyl benzoate	$C_6H_5CH_2O . COC_6H_5$	323–324°	A useful fixative for musk-ambrette or musk xylol.
Benzyl butyrate	$C_6H_5CH_2O . COC_3H_7$		A ' pineapple ' ester; used in many imitation fruit essences.
Benzyl cinnamate	$C_6H_5CH_2O . COCH{=}CHC_6H_5$	m.p. 39°	An ester with a good round apricot aroma; used mainly in perfumery as a contributive fixative.
Benzyl formate	$C_6H_5CH_2O . COH$	203°; 85°/10 mm.	Has a cinnamon-like flavour which is subdued; useful in Passion fruit types of fruit flavour.
Benzyl propionate	$C_6H_5CH_2O . COC_2H_5$	220°	Has odour similar to that of benzyl acetate, but is riper. Is used to ' tone ' the flavour of benzyl acetate in jasmine substitutes.
Benzyl *iso*valerate	$C_6H_5CH_2O . COC_4H_9$	135°/25 mm.	A powerful perfume – reminiscent of heather-honey.

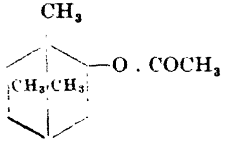
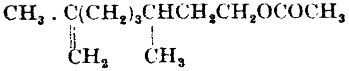
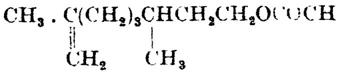
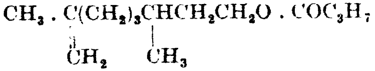
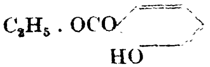
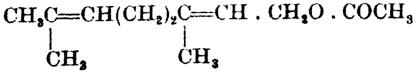
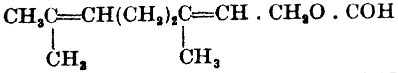
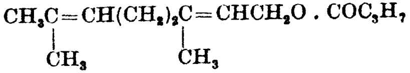
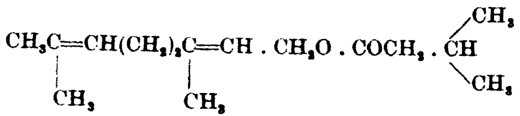
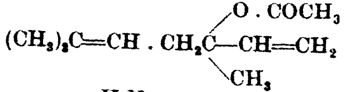
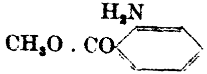
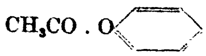
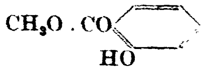
Bornyl acetate		225–226°	Has the pleasant odour of pineneedle oil, and is of value in soap perfumery.
Citronellyl acetate	 $CH_3 . \underset{CH_2}{\underset{\|}{C}}(CH_2)_3\underset{CH_3}{\underset{\vert}{C}}HCH_2CH_2OCOCH_3$	173°/34 mm.	Has an odour which recalls that of lavender and is therefore used in shading lavender and bergamot compounds for Eau de Cologne types.
Citronellyl formate	 $CH_3 . \underset{CH_2}{\underset{\|}{C}}(CH_2)_3\underset{CH_3}{\underset{\vert}{C}}HCH_2CH_2OCOCH$	98–100°/10 mm.	Similar to above.
Citronellyl propionate	 $CH_3 . \underset{CH_2}{\underset{\|}{C}}(CH_2)_3\underset{CH_3}{\underset{\vert}{C}}HCH_2CH_2O . COC_3H_7$	—	Has a distinct rose tone; is valuable in rose perfumes.
Ethyl phenylacetate	$C_2H_5O . COCH_2C_6H_5$	—	Used in various honey flavours and in the more sophisticated perfumes.
Ethyl benzoate	$C_2H_5O . COC_6H_5$	212°	Has a 'new mown' hay note which blends with that of coumarin and piperonal.
Ethyl butyrate	$C_2H_5O . COC_3H_7$	120°	A 'pineapple' ester: very useful in fruit essences.
Ethyl cinnamate	$C_2H_5OCOCH{=}CHC_6H_5$	271°	See 'benzyl cinnamate', which it resembles in odour. Valuable for Eaux de Cologne.
Ethyl formate	$C_2H_5 . OCO . H$	54·5°	Strong rum flavour.
Ethyl salicylate		231·5°	A refined 'wintergreen' odour.
Ethyl sebacate	$EtOOC . (CH_2)_8COOEt$	307–308°	An invaluable fruit essence component.
Geranyl acetate	 $CH_3\underset{CH_3}{\underset{\vert}{C}}{=}CH(CH_2)_2\underset{CH_3}{\underset{\vert}{C}}{=}CH . CH_2O . COCH_3$	242–245°	An extremely valuable rose-lavender perfume an active ingredient in many exotic floral types.
Geranyl formate	 $CH_3\underset{CH_3}{\underset{\vert}{C}}{=}CH(CH_2)_2\underset{CH_3}{\underset{\vert}{C}}{=}CH . CH_2O . COH$	104–105°/10 mm.	Reproduces the odour of the wild-rose; used for fresh rose types.
Geranyl propionate	 $CH_3\underset{CH_3}{\underset{\vert}{C}}{=}CH(CH_2)_2\underset{CH_3}{\underset{\vert}{C}}{=}CHCH_2O . COC_3H_7$	—	Resembles bergamot.

TABLE XLVI (*continued*)

Ester	Formula	B.P.	Comment
Geranyl *iso*valerate	 $CH_3\underset{\substack{\vert\\CH_3}}{C}{=}CH(CH_2)_2\underset{\substack{\vert\\CH_3}}{C}{=}CH.CH_2O.COCH_2.CH\begin{matrix}CH_3\\CH_3\end{matrix}$	138°/7 mm.	One of the most valuable rose-esters; adds a 'realistic note' to rose-perfumes.
Linalyl acetate	 $(CH_3)_2C{=}CH.CH_2\overset{O.COCH_3}{\underset{CH_3}{C}}{-}CH{=}CH_2$	220°; 97°/10 mm.	Occurs in numerous real flower oils; is invaluable in lily of the valley, lavender and bergamot perfumes.
Methyl anthranilate		—	Found in tuberose, neroli, ylang-ylang, gardenia and jasmine and used in their reproduction.
Methyl benzoate		199°	Niobe oil. Used in meadowsweet perfumes, but has a tendency to be overpowering.
Methyl cinnamate	$CH_3O.COCH{=}CHC_6H_5$	263°	A pleasant odour reminiscent of bergamot and apricot; used as a fixative for Eaux de Cologne.
Methyl salicylate		222°	A strongly odorous body; resembles intensely the natural oil of wintergreen in which it is largely present.
Phenylethyl acetate	$C_6H_5CH_2CH_2O.COCH_3$	224°	Has a well developed peach odour; used to give 'colour' (i.e. a special type of smell) to floral perfumes.
Phenylethyl butyrate	$C_6H_5CH_2CH_2O.COC_3H_7$	—	Has the characteristic tea-rose odour, invaluable in white-rose and carnation.
Phenylethyl formate	$C_6H_5CH_2CH_2O.COH$	95°/10 mm.	Reminiscent of chrysanthemums; used in autumnal, 'out-of-door' types of perfume.
Phenylethyl propionate	$C_6H_5CH_2CH_2O.COC_2H_5$	—	A useful 'heavy' rose type.
Phenylethyl valerate	$C_6H_5CH_2CH_2O.COC_4H_9$	—	Has the characteristic perfume of freshly crushed sweet-briar leaves. Lends freshness to rose perfumes.

The reaction is carried out in the vapour phase in the presence of a catalyst such as activated zinc phosphate. A mercury catalyst is used in the liquid-phase condensation of acetylene with acetic acid to give vinyl acetate :—

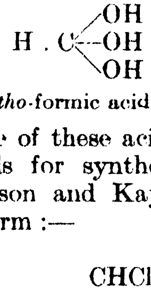
$$CH{\equiv}CH + CH_3COOH \longrightarrow CH_2{=}CH \,.\, COOCH_3 \quad \text{Vinyl acetate}$$

a reaction of considerable importance in the plastics industry.

The properties of esters are mainly concerned with (*a*) their hydrolysis to the original acid and alcohol, (*b*) their use as synthetic raw materials and (*c*) their organoleptic properties. Neither of the former matters need further discussion here ; the hydrolysis of esters is dealt with in Vol. III and the synthetic uses of esters is the main subject of Appendix III to this chapter. A few words may be added concerning the organoleptic properties, since esters comprise among them some of the most agreeably odorous compounds known. Ever since their first ' pear drop ' was made with crude amyl acetate, esters have been used for the manufacture of essences designed to imitate fruit flavours—with more or less success ; some of the modern esters such as allyl caproate come very near indeed to the natural flavours (in this case, that of the pineapple), and when skilfully blended are a pleasant contribution to the pleasure we derive from taste. In Table XLVI are collected together a few of the esters which are valued for their odour, together with a very brief description of their use.

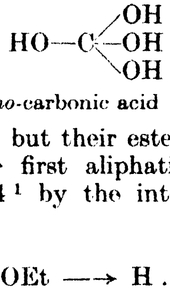
ORTHO-ESTERS

All carboxylic acids are, theoretically, the anhydrides of the *ortho*-acids which for the purposes of this book may be divided into three classes :—

I. 

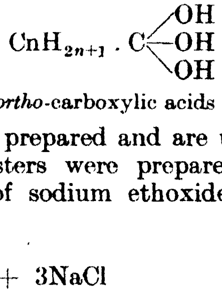
$$H \,.\, C(OH)_3$$

ortho-formic acid

II. 

$$HO{-}C(OH)_3$$

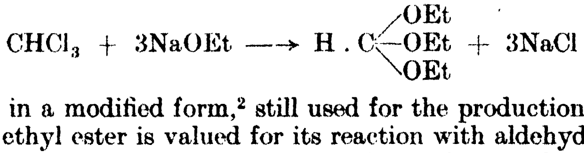
ortho-carbonic acid

III. 

$$C_nH_{2n+1} \,.\, C(OH)_3$$

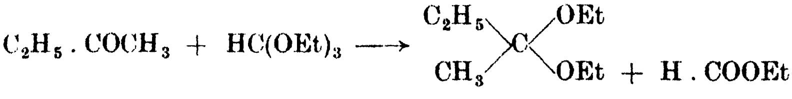
The *ortho*-carboxylic acids

None of these acids exists, but their esters can be prepared and are useful materials for synthesis. The first aliphatic *ortho*-esters were prepared by Williamson and Kay in 1854 [1] by the interaction of sodium ethoxide and chloroform :—



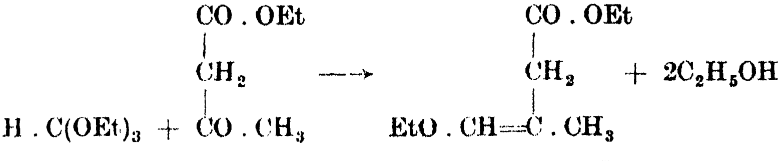
$$CHCl_3 + 3NaOEt \longrightarrow H \,.\, C(OEt)_3 + 3NaCl$$

The method is, in a modified form,[2] still used for the production of ethyl *ortho*-formate. The ethyl ester is valued for its reaction with aldehydes and ketones (particularly the latter) whereby acetals are obtained in good yield and uncontaminated—except by ethyl formate :—



$$C_2H_5 \,.\, COCH_3 + HC(OEt)_3 \longrightarrow (C_2H_5)(CH_3)C(OEt)_2 + H \,.\, COOEt$$

Further, ethyl *ortho*-formate reacts readily with the hydrogen atoms of an active methylene group yielding alkoxy-methylene groups of a useful contour :—



$$H \,.\, C(OEt)_3 + CH_3 \,.\, CO \,.\, CH_2 \,.\, CO \,.\, OEt \longrightarrow EtO \,.\, CH{=}C(CO \,.\, CH_3) \,.\, CH_2 \,.\, CO \,.\, OEt + 2C_2H_5OH$$

---

[1] Williamson and Kay, *Proc. Roy. Soc.*, 1854, **7**, 135.

[2] Herzog and Dreger, *Org. Syntheses*, 1925, **5**, 55.

The *ortho* esters are also available for a peculiar synthesis of the acetylenic aldehydes. When a substituted acetylene magnesium chloride reacts with ethyl *ortho*-formate, the following transformations occur leading to the aldehyde :—

$$\begin{array}{l} CH_3CH_2C{\equiv}CMgCl \;+\; CH(OEt)_3 \\ \downarrow \\ CH_3CH_2C{\equiv}C\,.\,CH(OEt)_2 \\ \downarrow \\ CH_3CH_2C{\equiv}C\,.\,CHO \end{array}$$

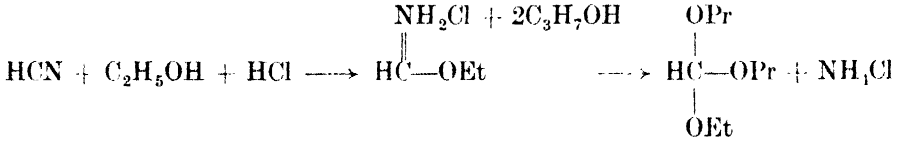
Ethyl *ortho*-carbonate can only be obtained in very small yield, if at all, from carbon tetrachloride and sodium ethoxide. Bassett[1] found that chloropicrin gave the tetra ester, with loss of its nitro group, in moderate yield :—

$$CCl_3NO_2 + 4EtONa \longrightarrow C(OEt)_4 + 3NaCl + NaNO_2$$

Rose[2] improved Bassett's method and improved the yield to about 30 per cent. of the theoretical figure and Hill[3] obtained much higher yields of the methyl, ethyl, butyl, amyl and β-phenyl ethyl *ortho*-carbonic esters. Connolly and Dyson[4] showed that *ortho*-carbonates could be obtained equally well from thiocarbonyl tetrachloride :—

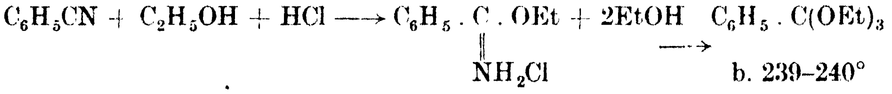
$$CCl_3\,.\,SCl + 4NaOEt \longrightarrow EtO\,.\,S\,.\,C(OEt)_3 + 4NaCl \longrightarrow C(OEt)_4 + S$$

The majority of *ortho*-carboxylic acids have been made by one or other modification of the imino-ester method, originated by Pinner[5] in 1883. Hydrogen cyanide, an alcohol, and hydrogen chloride are allowed to react in absolute ether ; a series of reactions leads to an imino-chloride ester, which on warming with alcohol gives an *ortho*-formate



$$HCN + C_2H_5OH + HCl \longrightarrow \overset{NH_2Cl}{\overset{\|}{HC}}{-}OEt \;\; \overset{+\,2C_3H_7OH}{\longrightarrow} \;\; \underset{OEt}{\underset{|}{\overset{OPr}{\overset{|}{HC}}}}{-}OPr + NH_4Cl$$

If a nitrile is used, a series of carboxylic *ortho*-esters is obtained



$$C_6H_5CN + C_2H_5OH + HCl \longrightarrow C_6H_5\,.\,\underset{NH_2Cl}{\underset{\|}{C}}\,.\,OEt \;\overset{+\,2EtOH}{\longrightarrow}\; \underset{\text{b. }239\text{–}240^\circ}{C_6H_5\,.\,C(OEt)_3}$$

A series of such compounds was prepared by Brooker and White.[6]

APPENDIX I

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[1] Bassett, *Chem. News*, 1863, **7,** 158 ; *Ann.*, 1864, **132,** 54.

[2] Rose, *ibid.*, 1880, **205,** 249.

[3] Hill. Unpublished ; quoted on p. 19 of H. W. Post's "Ortho Esters". See Appendix I.

[4] Connolly and Dyson, *J.C.S.*, 1937, 828.

[5] Pinner, *Ber.*, 1883, **16,** 352.

[6] Brooker and White, *J.A.C.S.*, 1935, **57,** 2480.

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APPENDIX II

THE TANNINS

The art of tanning has been known from time immemorial, and is an example of a process which has remained essentially the same since its discovery in antiquity. In essence, the process of tanning involves the steeping of a prepared animal skin (hair and flesh removed) in an extract of certain barks, berries or galls with the object of rendering insoluble and waterproof the collagen protein, and so converting the skin to leather.

It is only natural, therefore, that enquiring minds have turned to a study of the active principles of such barks—the tannins. Pliny mentions the use of slips of cane dipped in extract of nut-galls to detect the adulteration of verdigris with green vitriol, and observations of this kind led to the discovery and use of iron inks.

Tannins are widely distributed in the plant world, and are to be found mainly in trees and shrubs; annual plants seldom exhibit any tannin. In general, it may also be said that if a plant contains tannin at all, the material will be diffused throughout the whole structure, being carried in solution in the sap; nevertheless, there is a marked tendency for accumulation of tannin in the outer structures—the bark, the root stocks, in woody tissue and in the outer part of fruits. The suggestion has been made that this tannin accumulation at surfaces is protective in the sense that it causes an astringency of taste which makes the plant unpalatable, but it is unlikely that this is the prime purpose of these substances, since many are closely related to plant pigments and other substances of phytochemical importance. During ripening the astringency of fruit disappears; the tannin is either precipitated or is gathered up into special cells—tannin sacs, where it remains apart from the main flesh of the fruit, which having lost its astringency, is attractive to those animal and insect forces which are responsible for the dissemination of the seed. Ethylene hastens ripening and not only turns the colour of the fruit but accelerates the segregation of tannins.

The bite of certain insects on the leaves of Sumach (an Aphis) and of oak (Cynips) leads to an injury which brings about a large accumulation of tannins in a small pathological growth or gall. These galls are so rich in tannins as to constitute a source of the materials for industrial use.

The sources of tannins for economic purposes may be summarised as follows :

TABLE XLVII

SOURCE

I. *Fruits*

(*a*) Berries of *Terminalia chebula*, a Chinese plant ; gives the extract known as 'myrabolans'.

(*b*) Acorn cups of Grecian oak ; 'valonia', also grown in Asia Minor.

(*c*) Pods of *Cæsalpina* species ; these give 'divi-divi'.

II. *Barks*

(*a*) *Eucalyptus* species give Australian tannins ; *Eucalyptus occidentalis* also gives a tannin.

(*b*) *Tsuga canadensis*, the Hemlock spruce, gives a useful tannin.

III. *Wood*

(*a*) One of the most important tannins is that from *Quebracho Colorado* (Argentine) known as 'quebracho'.

(*b*) Chestnut (*Castanea vesca*) gives a tannin.

IV. *Leaves*

Sumach (*Rhus* species. . *cotinus* and *coriaria*), give a valuable tannin.

V. *Galls*

From insect-bitten leaves of *Quercus* and *Rhus*. "Aleppo galls" are from *Quercus infectoria* and Chinese galls from *Rhus semilata*.

In addition, innumerable plants, tea for example, contain tannin in quantities too small for commercial extraction, e.g., willow (*salix triandra*), larch (*larix europœa*), cherry (*prunus cerasus*) all give a bark tannin, as also does the wood of *Hamamelis virginiana*, and the root tissue of the Pomegranate (*Punica granatum*).

Chemically speaking, the classification of tannins into groups is best done according to the system of Perkin and Everest.[1] Three groups are recognised :—

(1) *Gallotannins or Depsides* are those which on hydrolysis with dilute acids yield gallic or digallic acid and a sugar.

(2) *Ellagotannins*, those which on hydrolysis yield ellagic acid and a sugar.

(3) *Catechol tannins* (*Phlobotannins*), substances which on boiling with dilute acids give a red precipitate or 'phlobaphene'. These are called by Freudenberg 'condensed' tannins, since their nuclei are held together by carbon links and not by the simple ester links of Classes (1) and (2).

Freudenberg's classification is similar, but he places the classes (1) and (2) of Perkin and Everest together as 'ester tannins'.

Whilst carrying out investigations on chloro-acetyl tyrosine, Fischer hit upon the method of protecting the hydroxyl groups of the tyrosine molecule without affecting the carboxyl group, by treating the substance with methyl or ethyl chloroformate ; these esters form a carbomethoxy or carbethoxy-phenol group with the hydroxyl, which protects the latter through subsequent reactions and may readily be removed by mild alkaline hydrolysis. This reaction forms the basis of much of Fischer's work in this field.

Fischer's work was first concerned with the linking together of galloyl and related groups in chains. It had been quite clear before Fischer came upon the scene that gallic and similar polyhydroxy acids were concerned with tannins and Fischer first elucidated the manner of their combination. To have a convenient reference to such complexes Fischer coined the term 'depside' ;

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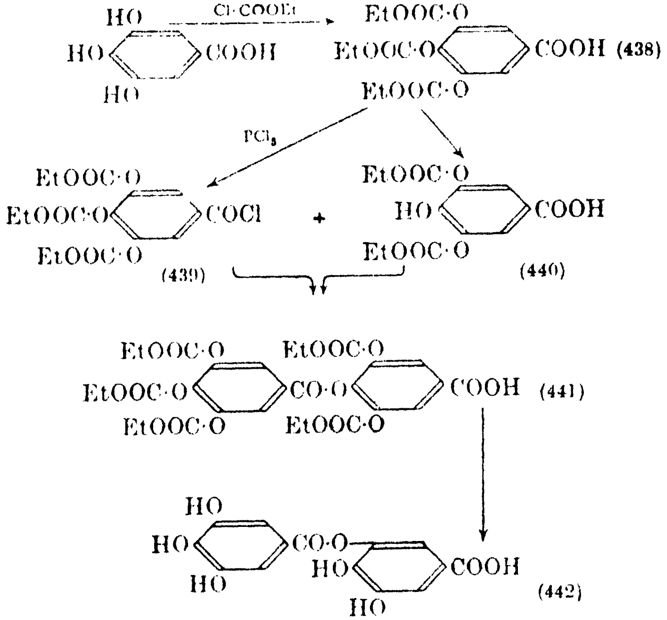
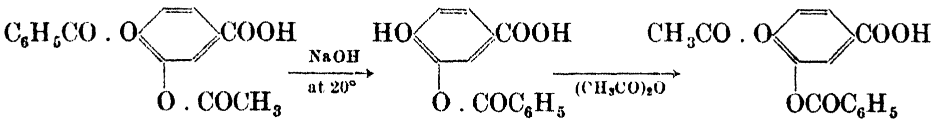
[1] See Appendix I.

a didepside was a combination of two gallic acid residues; a tri- or tetradepside involved three or four such groups. The didepsides, lecanoric and evernic acids, have already been described (p. 615). The main interest, insofar as ordinary tannins are concerned, is the didepside from gallic acid. This compound was closely investigated, and an unusual difficulty was encountered when a *m*-didepside was obtained instead of the expected *p*-compound. Thus :—



gallic acid is converted to its tricarboethoxy derivative (438) by treatment with ethyl chloroformate. This may be converted to the acid chloride (439) with phosphorus pentachloride and to the 3, 5-dicarboethoxy gallic acid (440) by treatment with one molecular proportion of cold caustic soda solution. The acid chloride and the partially hydrolysed ester condense to give the pentacarboethoxy didepside (441), but this on hydrolysis gives, not the expected *p*-digallic acid, but *m*-digallic acid (442). The authenticity of this unusual migration was established by Fischer in a number of comparative experiments with the benzoyl derivative of protocatechuic acid.

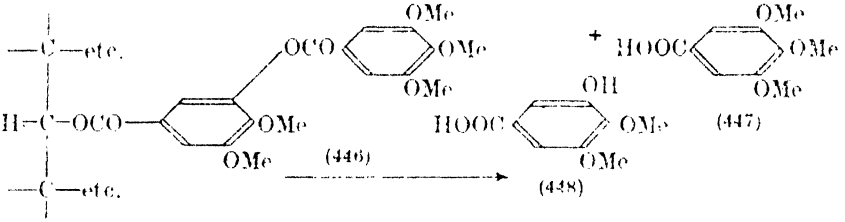


(443) (444) (445)

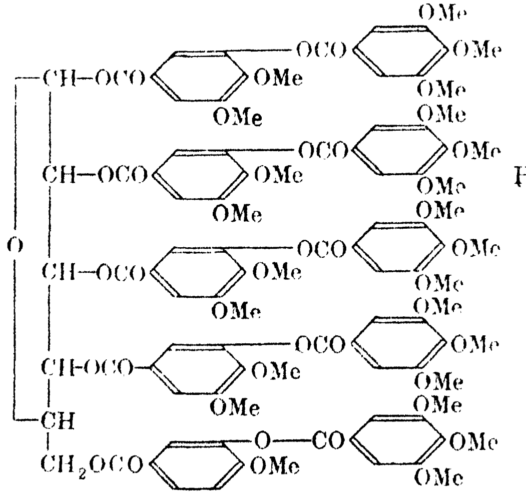
If *p*-benzoyl-*m*-acetyl protocatechuic acid (443) is hydrolysed with cold alkali, sufficiently strong to remove the acetyl group without disturbing the benzoyl group, *m*-benzoyl protocatechuic acid (444) is formed, not the expected *p*-benzoyl derivative; on acetylation of the benzoyl derivative, *p*-acetyl-*m*-benzoyl protocatechuic acid is obtained (445) demonstrably different from the compound (443). In this way, and by other means, the formula (442) of *m*-digallic acid was substantiated. It is a crystalline substance, m. 285°, which has an astringent taste and precipitates gelatine.

Fischer, having prepared a number of didepsides of which *m*-digallic acid is typical, then proceeded to an examination of tannin (or tannic acid) itself.

It had been reported by Strecker, working with Liebig,[1] that tannin contained glucose and for a long time tannin was regarded as a simple glycoside of gallic acid. Rochleder,[2] however, in 1858, pointed out that when tannic acid is purified the glucose content drops to about 4 per cent., but that further purification did not appear to decrease this proportion. Hlasiwetz [3] suggested that tannin might be a derivative of digallic acid. Fischer purified tannin by a series of extractions from faintly alkaline solutions with ethyl acetate, and after hydrolysis by 5 per cent. sulphuric acid at 100° for 70 hours, confirmed the view that glucose forms an inherent part of the tannin molecule, between 8 and 9 per cent. could always be recovered and the average figure corresponded to one molecule of glucose to ten of gallic acid. This naturally led Fischer to suppose that tannin was constituted as glucose, all five hydroxyl groups of which were esterified by digallic acid—a penta-*m*-digalloyl glucose. He thereupon set out to confirm the presence of *m*-digallic acid in the tannin molecule.


(446) (447) (448)

He was unsuccessful, although Herzig [4] and his co-workers succeeded in methylating tannin with diazomethane (part of the methylated molecule is shown in 446), and on hydrolysis they obtained trimethylgallic acid (447) and the unsymmetrical dimethylgallic acid (448). Fischer then determined to synthesise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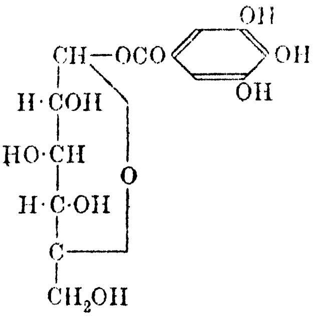
(450)

a penta-*m*-digalloyl glucose. He first attempted this through the pentacarbomethoxy-*m*-digallic acid, but the substance proved intractable and he turned his attention to pentamethyl-*m*-digallic acid, which he prepared without much difficulty and converted to the acid chloride. This was condensed with glucose yielding a penta(pentamethyl-*m*-digalloyl)glucose, which showed great similarity, if not complete identity, with completely methylated Chinese tannin. Fischer had, meanwhile, prepared satisfactory quantities of penta-acetyl-*m*-digallic acid, which was easily converted to its acid chloride, the latter condensing very satisfactorily with glucose in chloroform (in the presence of quinoline), the product being the pentacosamethyl derivative of tannin (449), which in turn gives on hydrolysis with caustic soda in acetone at 0° a substance, penta(*m*-digalloyl)glucose, which has a striking resemblance to Chinese tannin. The absence of very definite physical characteristics and the inability of ultimate analysis to distinguish between closely related compounds of high M.W. made it difficult to establish identity ; a difficulty which was by no means lessened by the variations in the natural product ; indeed, the variations in optical activity between purified samples of natural Chinese tannin showed greater differences from their average value, than did the optical activity of Fischer's synthetic product. The natural product is probably a mixture not only of completely and incompletely di-*m*-galloylated glucoses, but also of a variety of stereoisomers. Fischer has also emphasised the view that his own synthetic material is not homogeneous but that it contains more and less soluble portions.

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[1] Strecker, *Ann.*, 1854, **90**, 328.

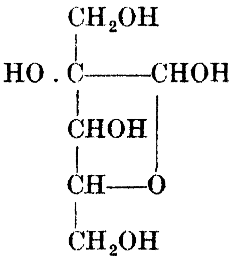
[2] Rochleder, *Ch. Zent.*, 1858, **3**, 579.

[3] Hlasiwetz, *Ann.*, 1867, **143**, 295.

[4] Herzig et al., *Ber.*, 1905, **38**, 989.

One simple tannin in which identity between the synthetic and natural products has been amply demonstrated is the glucogallic acid discovered by Gibson in rhubarb root (450). This was synthesised by Fischer and found identical with the natural product.

Another simple tannin which is crystalline is hamameli-tannin (452) in which the arborescent aldohexose hamamelose (451) has two hydroxyl groups esterified by gallic acid.



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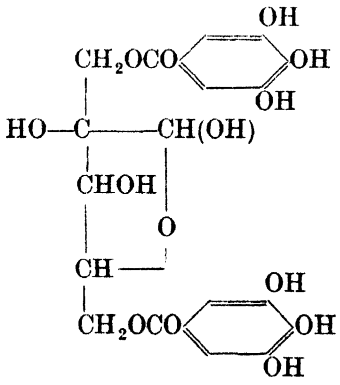


(452)

The tannins from twig-galls are more complex than Chinese tannins and hydrolytic experiments show that a part of their structure is composed of ellagic acid molecules. No synthetic work has, as yet, been accomplished in this section of the subject.

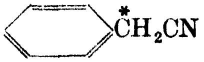
The third group of tannins, the catechins, are flavone derivatives and have already been discussed (Appendix IV, Chap. V) in connexion with their relation to cyanidin and the phloroglucinol anthocyanidins.

APPENDIX III

THE ACTIVE METHYLENE GROUP

The immediate proximity of a carbonyl group to a methylene group increases the lability of the hydrogen atoms of the latter ; the material in the main body of this chapter contains innumerable instances of reactions taking place at the α-carbon atom of an acid or ester. The —CN group is even more powerful than the carbonyl group in this respect and nitriles such as

$CH_3\overset{*}{C}H_2CN$ $\qquad$ $CH_3(CH_2)_n\overset{*}{C}H_2CN$



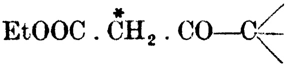
have a strikingly enhanced reactivity in the α-methylene group. This takes the form of ability to form sodio derivatives by replacement of a single atom of hydrogen with sodium, and power to condense directly with aldehydes to form unsaturated derivatives.

The 'active methylene group' (as such groups are called) (*), is shown to a remarkable degree in such groups as lie between two carbonyl groups or between one carbonyl or one cyano group. The following types can be distinguished.

I. $EtOOC\,.\,\overset{*}{C}H_2\,.\,CN$ — α-Cyano esters

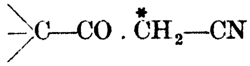
II. $EtOOC\,.\,\overset{*}{C}H_2\,.\,COOEt$ — Malonic esters

III.



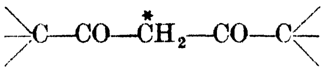
β-Ketonic esters

IV.



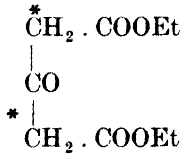
β-Ketonic nitriles

V.

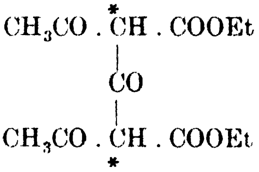


β-Diketones

All these types show the characteristic behaviour of the active methylene group at the point marked (*), and one or more of any of them can recur more than once in the same compound—e.g., acetone dicarboxylic ester, and its diacetyl derivative—both of which have two active groups. For the sake of



$$\begin{array}{l}\overset{*}{C}H_2\,.\,COOEt\\ |\\ CO\\ |\\ \overset{*}{C}H_2\,.\,COOEt\end{array}$$

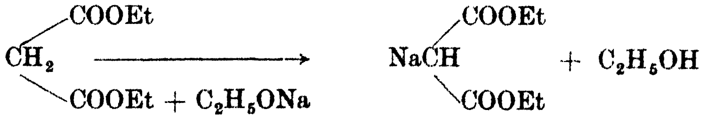


$$\begin{array}{c}CH_3CO\,.\,\overset{*}{C}H\,.\,COOEt\\ |\\ CO\\ |\\ CH_3CO\,.\,\underset{*}{C}H\,.\,COOEt\end{array}$$

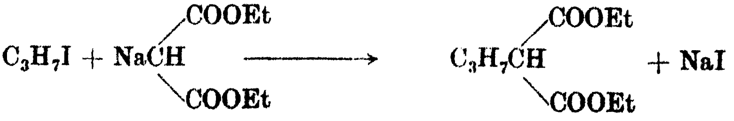
clarity it is proposed to divide the consideration of these substances into classes corresponding to the five groups above, and to commence with malonic ester derivatives.

Malonic Ester Derivatives

Conrad,[1] in his researches which initiated our knowledge of malonic ester syntheses, observed the formation of a monosodium derivative, which is a crystalline substance of definite structure and composition. It could be obtained either by the action of sodium on malonic ester or of a solution of sodium ethoxide in ethanol,



In either case crystals of the sodio derivative are formed, and these will react with an alkyl iodide by a reaction which it is customary to write thus :—



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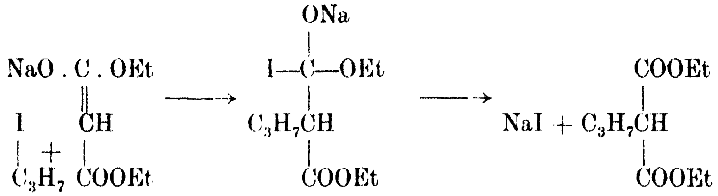
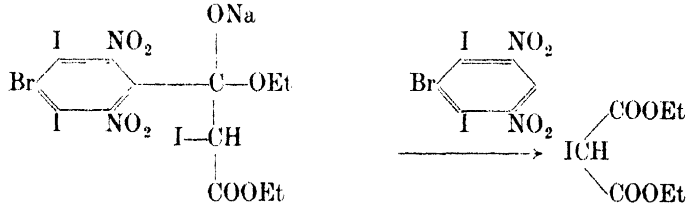
[1] Conrad, *Ann.*, 1880, **204**, 127.

It was Michael[1] in 1888 who drew attention to the possibility of the sodio malonic ester being the derivative of the enolic form, and it was Nef and Liebermann[2] who expressed the reaction above in the following manner :—



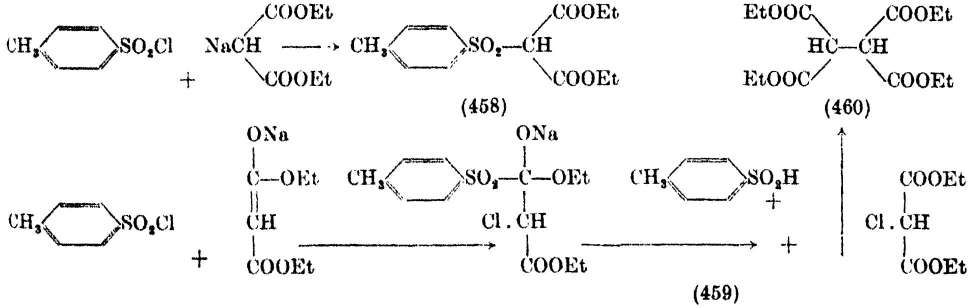
(453) (454) (455)

in which the sodio derivative has the enolic form ; and in which the reaction is represented, not as a double decomposition, but as an addition, the intermediate unstable form (457) being postulated. Here the matter rested as, although the final result was the same, no critical method of testing the two alternative conceptions was available. Nearly twenty years later Jackson and Whitmore[3] noted that when 1, 3, 5-tri-iodo-2-bromo-4, 6-dinitrobenzene was allowed to react with the sodio-derivative of malonic ester definite evidence of the formation



(456) (457)

of an enolic derivative of the structure (456) was obtained which decomposes with the formation of iodomalonic ester and a bromo-di-iodo-dinitrobenzene (457). This conception is further strengthened by the work of Kohler and MacDonald,[4] who observed that when *p*-toluene sulphonchloride reacts with sodio-malonic ester the reaction takes both courses ; yielding *p*-toluene sulphomalonic ester (458) in small quantity, the main product being *p*-toluene sulphinic acid (459)



(458) (460) (459)

and ethane tetracarboxylic ester (460) which results from the combination of two molecules of chloromalonic ester in the presence of excess of sodium.

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[1] Michael, *J. Pr. Chem.*, 1888, **37**, 496.

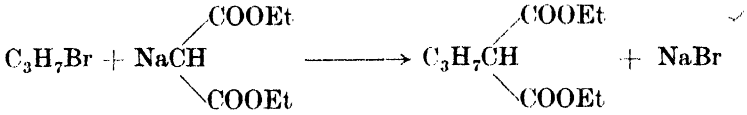
[2] Nef, *Ann.*, 1891, **266**, 67 ; 1892, **270**, 334 ; 1899, **308**, 284. Liebermann, *Ber.*, 1894, **27**, 292.

[3] Jackson and Whitmore, *Ber.*, 1913, **46**, 67.

[4] Kohler and MacDonald, *Am. Chem. J.*, 1899, **22**, 27.

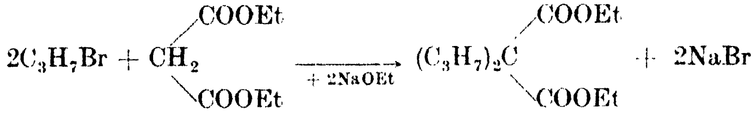
In dealing with the following developments of the malonic acid synthesis, the conventional formula will be used for the sodio-derivative.

(1) Halogen compounds react readily with sodio-malonic ester. Thus, alkyl halides yield alkyl malonic esters by the following reaction :—



$$C_3H_7Br + NaCH(COOEt)_2 \longrightarrow C_3H_7CH(COOEt)_2 + NaBr$$

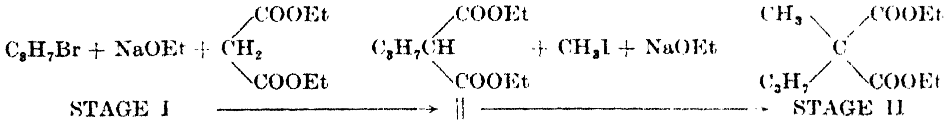
Care must be taken in such reactions that the sodium and alkyl halide are present only in the correct monomolecular proportions, since, whilst it is very doubtful whether malonic ester forms a disodio derivative,[1] it is quite easy to obtain the dialkyl halide by adding a second mole of NaOEt and alkyl halide. The reaction then takes the course :—



$$2C_3H_7Br + CH_2(COOEt)_2 \xrightarrow[+\,2NaOEt]{} (C_3H_7)_2C(COOEt)_2 + 2NaBr$$

A small quantity of dialkylmalonic ester is always produced in the former reaction, but is easily separated from the mono-derivative by fractional distillation.

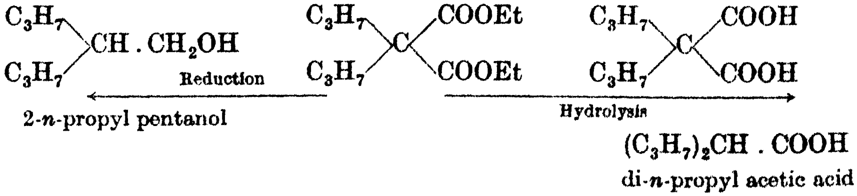
In the preparation of mixed derivatives, e.g., methyl-*n*-propyl malonic ester, the larger group should be introduced first, and it is preferable to isolate and purify the monopropyl malonic ester before proceeding with the introduction of the second group.



$$C_3H_7Br + NaOEt + CH_2(COOEt)_2 \xrightarrow{\text{STAGE I}} C_3H_7CH(COOEt)_2 + CH_3I + NaOEt \xrightarrow{\text{STAGE II}} (CH_3)(C_3H_7)C(COOEt)_2$$

Theoretically, it seems that one could wait until the first reaction had subsided with the formation of the propyl derivative, and then add another charge of methyl halide and sodium ethoxide ; if this is attempted, some interchange of radicles takes place, and a mixture of dimethyl, dipropyl and methylpropyl malonic esters ensues with consequent loss of yield and difficulty of separation.

Hydrolysis of these substituted malonic acids is invariably attended with the formation of a monocarboxylic acid by elimination of carbon dioxide. Vigorous reduction of the esters yields an alcohol :—



$$(C_3H_7)_2CH\,.\,CH_2OH \xleftarrow{\text{Reduction}} (C_3H_7)_2C(COOEt)_2 \xrightarrow{\text{Hydrolysis}} (C_3H_7)_2C(COOH)_2 \longrightarrow (C_3H_7)_2CH\,.\,COOH$$

2-*n*-propyl pentanol

di-*n*-propyl acetic acid

In this way an approach to acids and alcohols is available.

(2) The interaction of a dihalogen compound with sodiomalonic ester is capable of proceeding in several ways. Normally, when one dihalide

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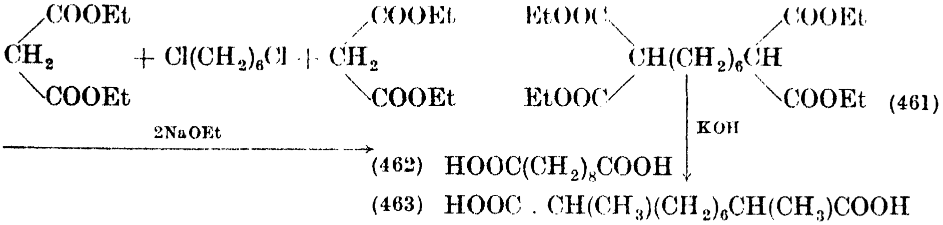
[1] Such a derivative was claimed by Bischoff, *Ber.*, 1884, **17**, 2782.

molecule is used for each pair of sodio malonic ester molecules the following change results :—

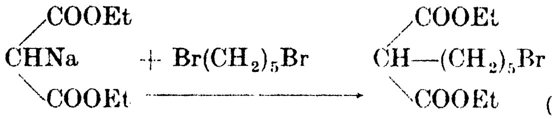


(461)

(462) $HOOC(CH_2)_8COOH$

(463) $HOOC . CH(CH_3)(CH_2)_6CH(CH_3)COOH$

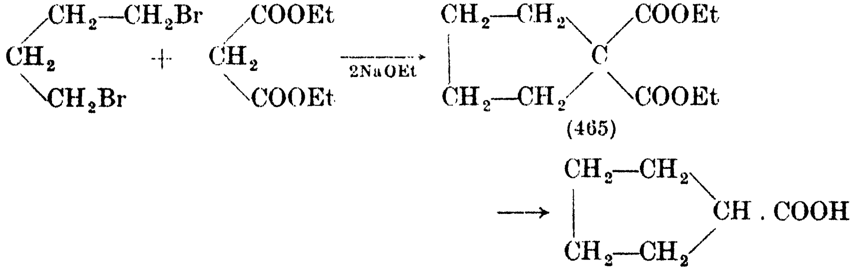
This gives an alkane tetracarboxylic ester (461) which can be hydrolysed to a dibasic acid (462). If an alkyl derivative of malonic ester (e.g., methyl malonic ester) is used the branched chain dibasic acid (463) is obtained. Under any circumstances a part of the reactants will stop short at the brom-alkyl ester (464) :—



(464)

The amount of this material is not a serious factor under normal conditions, but can be increased by raising the amount of halide present or by using the chlorobromide, if this be available, thereby making use of the difference in reactivity of the two halogens.

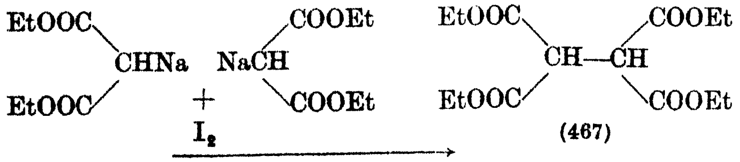
Yet a third method remains by which a dihalide may react with the sodio-ester, namely with the formation of a ring. It is not always possible to choose conditions such that the earlier reactions of this section are either eliminated from, or subordinated to, the formation of the ring compound. Thus, 1, 4-dibromobutane forms the *cyclo*pentane compound exclusively under all circumstances (465), whilst trimethylene dibromide can scarcely be induced to give more than mere traces of the *cyclo*-butane compound. The *cyclo*alkane dicarboxylic esters give the monocarboxylic acids normally when hydrolysed (466).



(465)

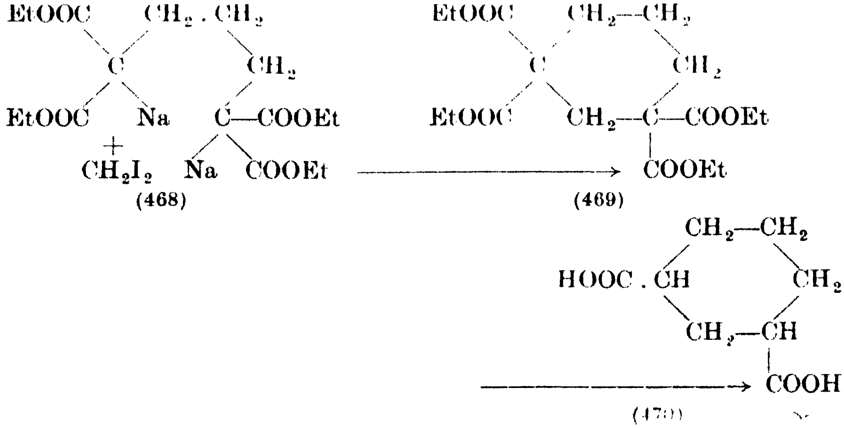
(466)

(3) When the sodio derivative of malonic ester is treated with iodine, two molecules become linked as in (467) to give ethane tetracarboxylic ester.



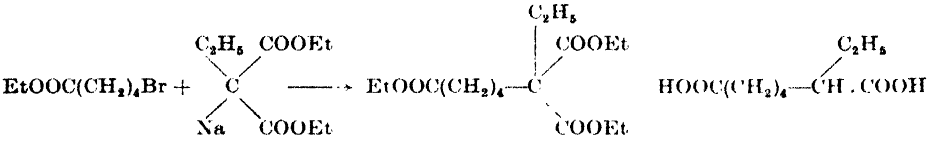
(467)

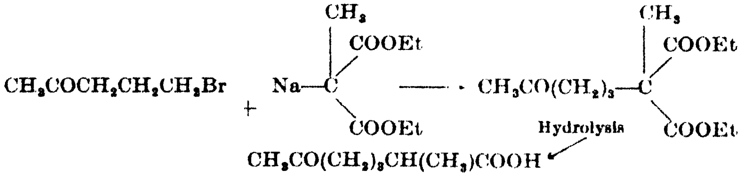
This procedure can be used to form rings in the following manner :—


(468) (469) (470)

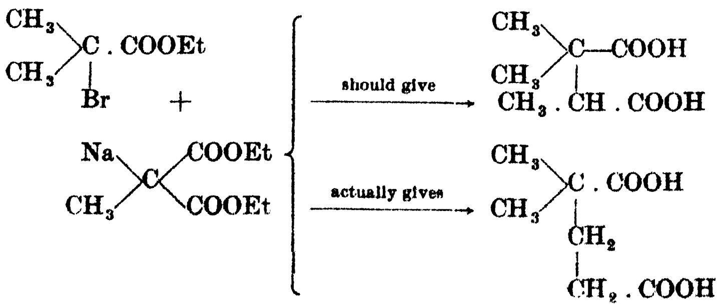
Two moles of sodiomalonic ester are allowed to react with one of a dibromide—trimethylene dibromide in (468)—to give the compound (468). This reacts with methylene di-iodide and two moles of sodium ethoxide to give the cyclic, tetracarboxylic ester (469) ; on hydrolysis, hexahydro-*iso*phthalic acid (470) is obtained ; had iodine itself been used in place of methylene iodide a *cyclo*pentane derivative would have been produced.

(4) The type of halide which will react with sodio-malonic ester is by no means confined to simple alkyl derivatives. Bromo esters or ketones will react similarly, giving a useful approach to the unsymmetrical dibasic acids and the higher keto acids. An example of each is given :—

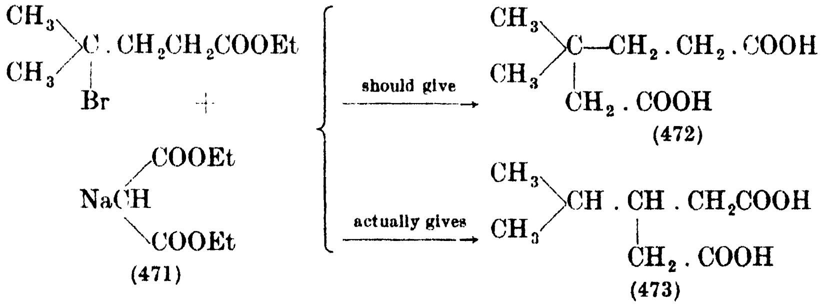

α-Ethyl pimelic acid.


2-Methylheptanone-6, acid-1

There are numerous deviations from this course ; if α-bromo*iso*butyric ester is condensed with sodio-methylmalonic ester, the expected trimethyl succinic acid is almost entirely absent, and α, α-dimethylglutaric acid is isolated.



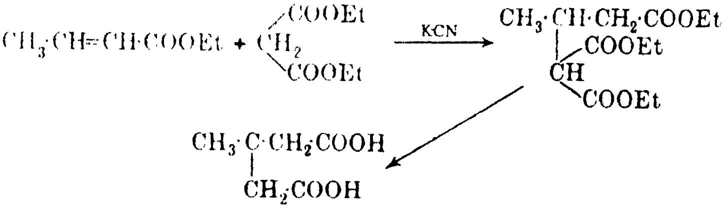
Conversely, γ-chloro*iso*caproic ester (471) gives with sodio malonic ester, α-*iso*propylglutaric acid (473), instead of the expected β, β-dimethyl adipic acid (472).



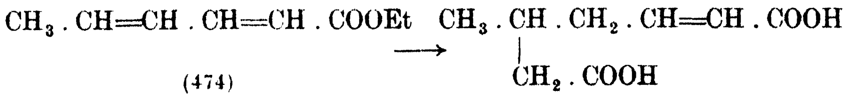
(471) (472) (473)

From these examples, it is clearly unsafe to accept the course of synthesis as evidence of structure, without independent characterisation.

(5) Most interesting structural types can be obtained by the condensation of unsaturated esters with sodio-malonic ester in the presence of potassium cyanide. The reaction takes the course :—



thus giving a β-substituted glutaric acid. The reaction is capable of wide variations ; cinnamic ester gives β-phenyl glutaric acid and the reaction proceeds equally well with mono-substituted malonic esters, which give α, β-di-substituted glutaric acids, and even such compounds as sorbic ester (474) will react normally the '4' double bond reacting in preference to the '2':

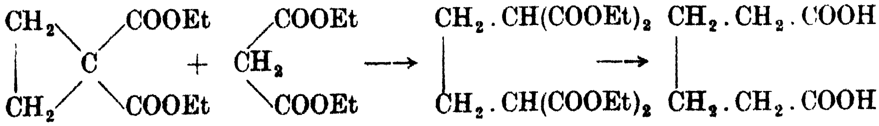


$$CH_3.CH{=}CH.CH{=}CH.COOEt \longrightarrow CH_3.\underset{\displaystyle CH_2.COOH}{CH}.CH_2.CH{=}CH.COOH$$

(474)

The reaction is complicated by 1, 6 and 1, 8 addition in the case of higher acids, so that there is a tendency for the double bond to migrate.[1]

It may be added here that the presence of a strained ring acts in a manner similar to unsaturation ; *cyclo*propane-1, 1-dicarboxylic ester reacts with malonic ester in the presence of potassium cyanide to give adipic acid :—



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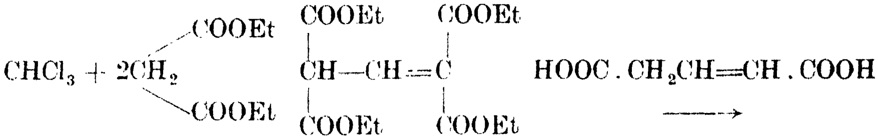
[1] A summary of the 1, 4 ; 1, 6 and 1, 8 additions is given by Kohler and Butler, *J.A.C.S.*, 1926, **48**, 1036.

(6) An interesting special case of the reaction of a halide with malonic ester is that of chloroform. Malonic ester with two equivalents of sodium ethylate is submitted to the dropwise addition of half an equivalent of chloroform. The reaction takes the course :—



$$\mathrm{CHCl_3 + 2CH_2(COOEt)_2 \longrightarrow \underset{(475)}{(EtOOC)_2CH{-}CH{=}C(COOEt)_2} \longrightarrow \underset{(476)}{HOOC.CH_2CH{=}CH.COOH}}$$

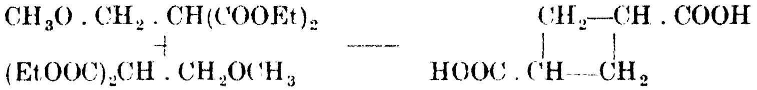
(475) (476)

giving a tetracarboxylic ester (475) which can be hydrolysed to glutaconic acid (476).

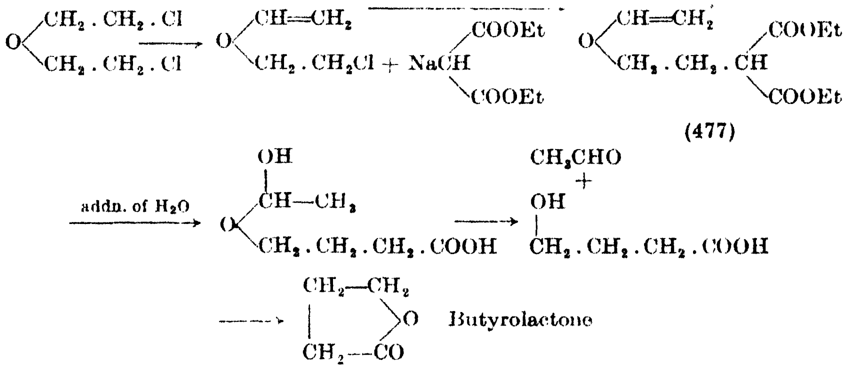
(7) Another special case is the action of chlorodimethyl ether. The first stage of reaction is quite as usual :—

$$\mathrm{CH_3.O.CH_2Cl + NaCH(COOEt)_2 \longrightarrow CH_3O.CH_2.CH(COOEt)_2}$$

but on attempting to hydrolyse the ester with hydrochloric acid two methoxy groups are eliminated and *cyclo*butane dicarboxylic acid results.



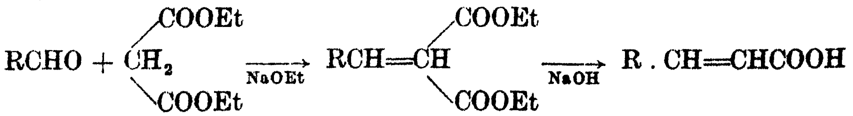
From dichloroethyl ether it is possible to obtain butyrolactone by the use of malonic ester. Vinyl-β-chloroethyl ether is obtained from the symmetrical β, β-dichloro ether, and reacted with sodio malonic ester to give the ester (477). On acid hydrolysis, butyrolactone is obtained by the various steps shown below :—



(477)

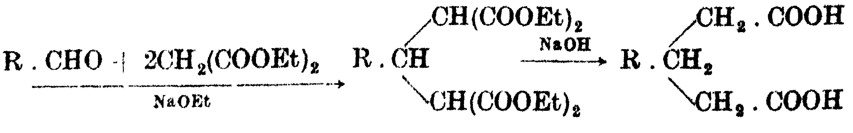
(8) *Reactions of Aldehydes and Ketones with Malonic Ester*

The reaction of an aldehyde with malonic acid can proceed in two ways (*a*) to form the unsaturated ester



$$\mathrm{RCHO + CH_2(COOEt)_2 \xrightarrow[NaOEt]{} RCH{=}C(COOEt)_2 \xrightarrow[NaOH]{} R.CH{=}CHCOOH}$$

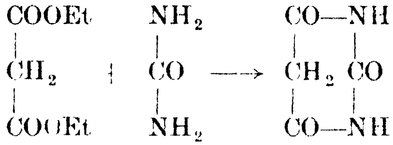
thus leading to the unsaturated acids, or (*b*) to form a tetracarboxylic ester :—



$$\mathrm{R.CHO + 2CH_2(COOEt)_2 \xrightarrow[NaOEt]{} R.CH\begin{cases}CH(COOEt)_2\\CH(COOEt)_2\end{cases} \xrightarrow{NaOH} R.CH_2\begin{cases}CH_2.COOH\\CH_2.COOH\end{cases}}$$

which, in turn, gives acids of the β-glutaric series. There is no need to use metallic sodium for these syntheses, as the reaction proceeds best in a secondary or tertiary base; diethylamine, piperidine and pyridine are commonly used; if it is desired to favour the unsaturated ester condensation, the use of acetic anhydride is recommended.

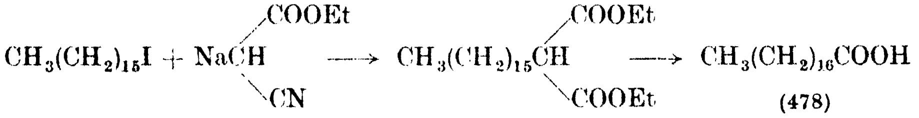
(9) Some mention must be made of the condensation of urea and malonic ester, which is not, however, an active methylene reaction but may conveniently be recorded here. The substance formed is malonyl urea or barbituric acid. This reaction is discussed in more detail in Chapter VII, Vol. II.



Cyanacetic Ester

Cyanacetic ester, and many other substances exhibiting the active methylene group, give reactions which are entirely analogous to those of malonic ester. It is not, therefore, proposed to catalogue all such examples, but merely to give examples of particular interest and to discuss such cases as are either anomalous, or where the new esters are able to extend the range of synthesis.

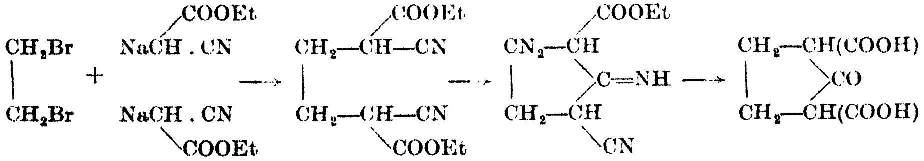
In the synthesis of simple acids by the interaction of alkyl halides, malonic ester is preferable, in many cases to cyanacetic ester; in some cases, however, the extra activity conferred by the cyano group and its smaller steric effect are of value in inducing reactions which are almost impossible with malonic ester, for example, *iso*-propyl malonic ester can only in rare instances be induced to allow the substitution of a second group on the active carbon atom; *iso*-propylcyanacetic ester, on the other hand, substitutes readily and thus gives alkyl-*iso*-propyl acetic acids on hydrolysis. Robinson[1] has used cyanacetic ester for condensation with the higher alkyl iodides and finds the reaction to give better yields than with malonic ester; acids up to *n*-octadecylic were prepared in this



$$CH_3(CH_2)_{15}I + NaCH\begin{smallmatrix}COOEt\\CN\end{smallmatrix} \longrightarrow CH_3(CH_2)_{15}CH\begin{smallmatrix}COOEt\\COOEt\end{smallmatrix} \longrightarrow CH_3(CH_2)_{16}COOH$$

(478)

way (478). Thorpe[2] found that with ethylene dibromide, cyclic compounds were obtained with cyanacetic ester, whereas, with malonic ester, an open-chain derivative was obtained :—



The anomalous reactions, described previously under malonic ester, in which the condensation of α-bromo*iso*butyric ester with sodio-methylmalonic ester gave dimethyl glutaric acid instead of the expected trimethyl succinic acids, can be avoided by the use of cyanacetic ester with which the reaction proceeds normally.

The Guareschi-synthesis.—One particular advantage which cyanacetic ester offers over malonic ester, is the ready condensation with ketones in the presence of ammonia to give a cyclic six-membered nitrogenous ring. The reaction proceeds :—

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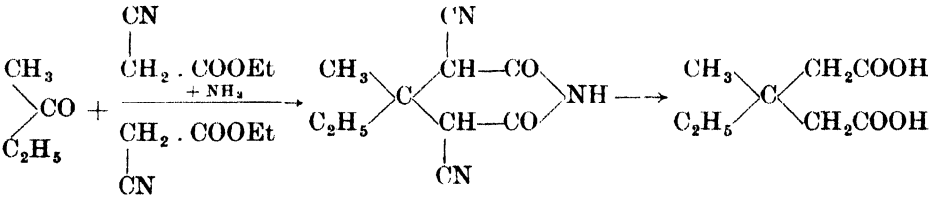
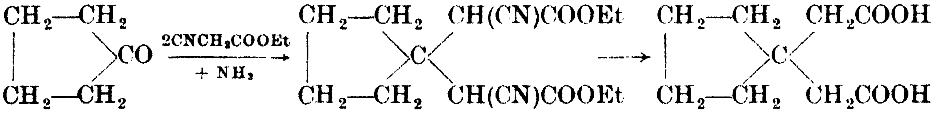
[1] Robinson, *J.C.S.*, 1924, **125**, 226.

[2] Best and Thorpe, *ibid.*, 1909, **95**, 685.



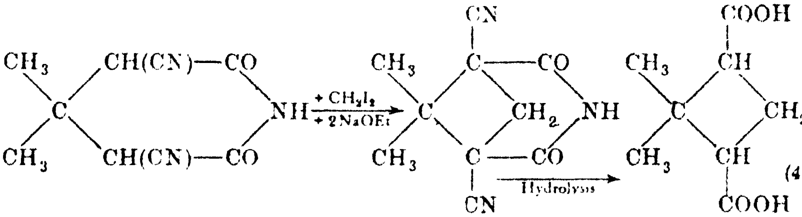
(479) (480)

and the Guareschi imide (479) can either be hydrolysed to a β, β-derivative of glutaric acid (480) or converted to a pyridine base. Cyclic ketones also give this reaction which affords a convenient approach to the *cyclo*alkane diacetic acids :—



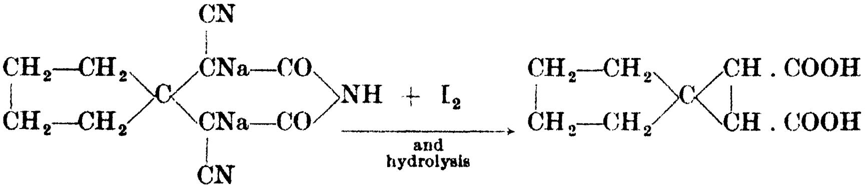
*cyclo*pentane, 1-diacetic acid

Further, it must be borne in mind, that the first Guareschi ester still has two active hydrogens capable of reacting with alkyl derivatives. Kerr [1] prepared, in excellent yield, *trans*-norpinic acid (481) from the acetone Guareschi ester thus :—



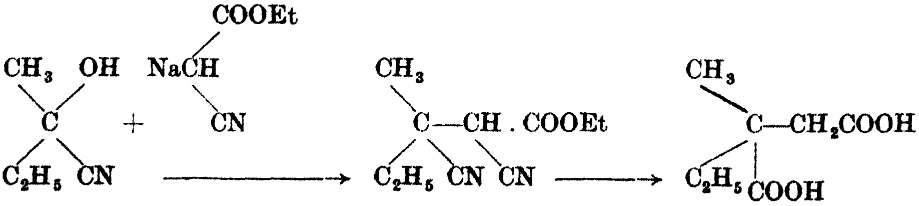
(481)

Spiro-compounds can also be prepared by the action of iodine or alkylene di-iodides on the Guareschi imides from cyclic ketones, e.g.,



Thorpe and Thole [2] used cyanacetamide in the presence of piperidine instead of the ester and succeeded in bringing the yields of glutaric acids up almost to the theoretical figures.

One type of compound which reacts readily with cyanacetic ester is the cyanhydrin ;



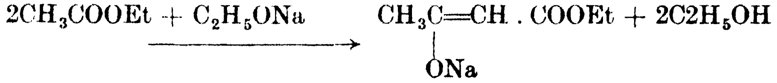
thus giving an approach to the α, α-substituted succinic acids.

[1] Kerr, *J.A.C.S.*, 1929, **51**, 614.

[2] Thorpe and Thole, *J.C.S.*, 1911, **99**, 422.

Acetoacetic and Related Esters

Geuther[1] discovered acetoacetic ester in 1853 during his researches on the action of sodium upon ethyl acetate, and Frankland and Duppa[2] experimented with the action of ethyl iodide on its sodium derivative. The reaction between two molecules of ethyl acetate in the presence of sodium ethoxide (often called a 'Claisen condensation' since Claisen investigated a wide range of such reactions) may be written :—

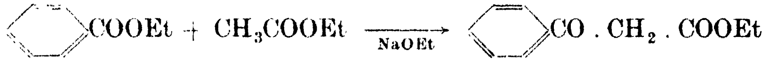


$$2CH_3COOEt + C_2H_5ONa \longrightarrow \underset{\displaystyle ONa}{CH_3C}{=}CH\,.\,COOEt + 2C2H_5OH$$

—indeed, Frankland and Duppa carried out their investigation on a sodio-derivative prepared in this way without the isolation of the intermediate ester. The reaction is a reversible one, and the difficulty of obtaining good yields of the ester is, in part, attributable to this factor. The scope of the acetoacetic ester condensation is wide; esters having hydrogen on the α-carbon atom condense readily, thus :—

$$(CH_3)_2CH\,.\,COOEt + (CH_3)_2CH\,.\,COOEt \longrightarrow (CH_3)_2CH\,.\,COC(CH_3)_2COOEt.$$

Mixtures are obtained when the two esters are different, unless one has no free α-hydrogen as in the case of ethyl formate, benzoate or oxalate, each of which affords excellent yields of the simple keto-esters, e.g., benzoyl-acetic ester :—



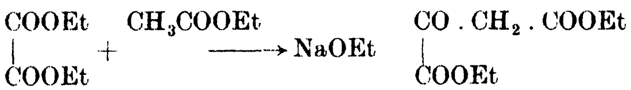
Examples in which ethyl formate is used are :—

(1) Formyl acetic ester. $HCOOEt + CH_3COOEt \longrightarrow H\,.\,CO\,.\,CH_2\,.\,COOEt$

(2) Formyl crotonic ester. $HCOOEt + CH_3CH{=}CH\,.\,COOEt$
$\longrightarrow H\,.\,CO\,.\,CH_2CH{=}CH\,.\,COOEt$

It is to be noted that in the second example, condensation of the formic ester takes place with a γ hydrogen atom, instead of the α-hydrogen. This is also observable in the condensation of formic ester and ethyl sorbate, where the terminal hydrogen reacts.

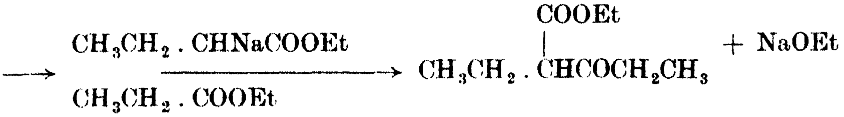
An example of the use of oxalic ester is the formation of oxalacetic ester, a synthetic agent of considerable value :—



$$\begin{array}{l}COOEt\\ |\\ COOEt\end{array} + CH_3COOEt \xrightarrow{} NaOEt \quad \begin{array}{l}CO\,.\,CH_2\,.\,COOEt\\ |\\ COOEt\end{array}$$

The range of ketonic esters available for synthesis has been materially enlarged by the use of sodium triphenylmethyl as a reagent. Thus, by allowing an ester to react with a molecule of sodium triphenyl methyl, it can be converted quantitatively to its sodium compound, which is then able to react with a second, but different ester; in this way, a tolerably good yield of unsymmetrical keto esters may be obtained.

$$CH_3CH_2CH_2\,.\,CO\,.\,OEt + (C_6H_5)_3CNa \longrightarrow CH_3CH_2CHNa\,.\,COOEt + (C_6H_5)_3CH$$



$$\longrightarrow \frac{CH_3CH_2\,.\,CHNaCOOEt}{CH_3CH_2\,.\,COOEt} \longrightarrow \begin{array}{l}COOEt\\ |\\ CH_3CH_2\,.\,CHCOCH_2CH_3\end{array} + NaOEt$$

---

[1] Geuther, *Jahresb. Chem.*, 1863, 323.
[2] Frankland and Duppa, *Phil. Trans.*, 1866, **156**, 37.

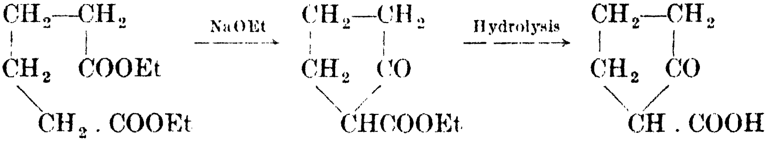
A further method of preparing keto acids, especially those with a long initial hydrocarbon chain, is by digesting a ketone with sodium ethoxide and a large excess of ethyl carbonate.

$$CH_3(CH_2)_6COCH_3 + C_2H_5O\,.\,COOEt \longrightarrow CH_3(CH_2)_6COCH_2COOEt.$$

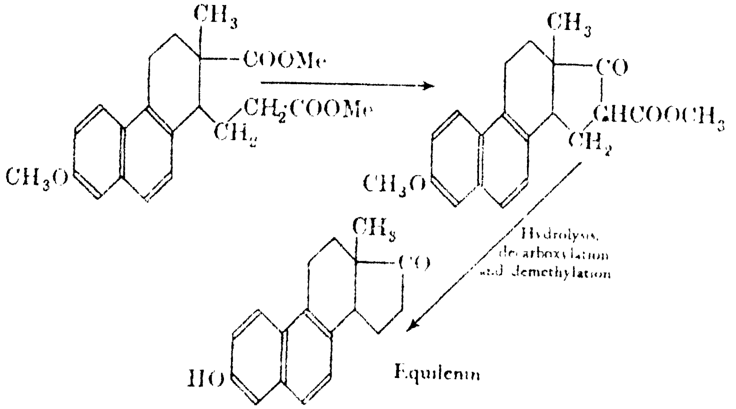
A further method for preparing esters of acetoacetic acid is feasible, on account of the large scale manufacture of diketen ; the latter substance will react with alcohols giving almost theoretical yields of acetoacetic ester :—

$$CH_3COCH{=}CO \xrightarrow[H-OEt]{} CH_3\,.\,COCH_2\,.\,COOEt.$$

It may also be remarked that an internal acetoacetic ester condensation can be obtained between two ends of a long-chain keto ester. This reaction is known as " Dieckmann's Reaction ", and although of interest with single rings, as for example, the conversion of ethyl adipate to *cyclo*pentanone carboxylic acid :—



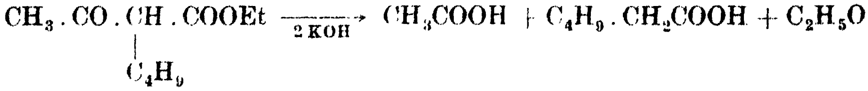
it is, however, of considerable value in the *cyclo*pentano-phenanthrene series ; this reaction enabled Bachmann and others[1] to prepare equilenin in almost theoretical yield, thus :—



The Decompositions of Acetoacetic Ester

The tautomerism exhibited by acetoacetic ester is dealt with in Chapter IV, Vol. III. This appendix is mainly concerned with its various decompositions ; when acetoacetic ester or its homologues are submitted to the action of alkalies they break down to give an acid :—

(a) $CH_3\,.\,COCH_2COOEt \xrightarrow[2\,KOH]{} CH_3COOH + CH_3COOH + C_2H_5OH$


(b) $CH_3\,.\,CO\,.\,\underset{\displaystyle C_4H_9}{\underset{|}{CH}}\,.\,COOEt \xrightarrow[2\,KOH]{} CH_3COOH + C_4H_9\,.\,CH_2COOH + C_2H_5O$

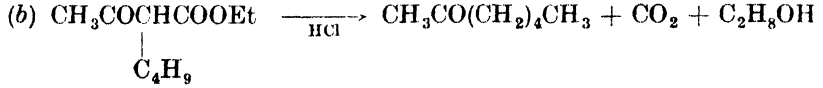
This process is referred to as *acid* hydrolysis in view of the nature of the product formed, and despite the fact that an alkali is used to perform the reaction.

---

[1] Bachmann, Cole and Wilds, *J.A.C.S.*, 1940, **62**, 835.

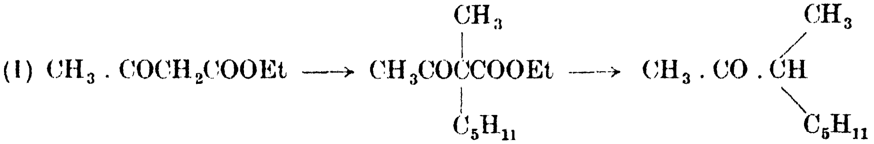
When heated with acids, acetoacetic ester and its homologues break down into ketones :—

(a) $CH_3COCH_2COOEt \xrightarrow[HCl]{} CH_3COCH_3 + CO_2 + C_2H_8OH$

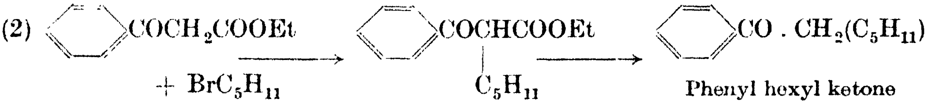


$$(b)\ CH_3CO\underset{\substack{|\\ C_4H_9}}{C}HCOOEt \xrightarrow[HCl]{} CH_3CO(CH_2)_4CH_3 + CO_2 + C_2H_8OH$$

This is referred to as keto-hydrolysis, and affords a very valuable method of building up ketones, which are not available from the malonic and cyanacetic series. Two examples will give some indication of the scope of ketone synthesis, but in the first place it must be premised that the active methylene group of the acetoacetic and other β-ketonic esters is capable of affording a sodio-derivative and a synthesis of β-substituted derivatives similar to that exhibited by the malonic series. Thus :—

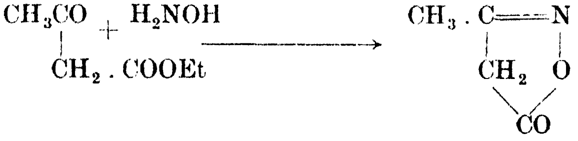


3-Methyloctanone-2

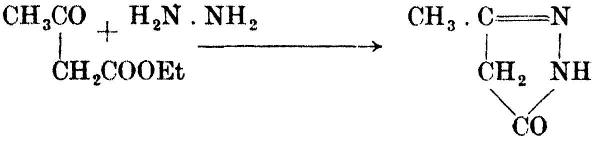


Phenyl hexyl ketone

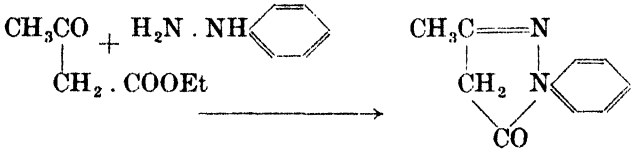
Acetoacetic ester will condense through the keto group with substances such as hydroxylamine and phenylhydrazine, leading to cyclic compounds of some importance. Thus with hydroxylamine it gives methyl oxazolone :—



Methyl oxazolone



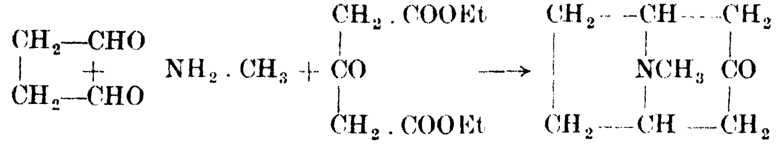
Methyl pyrazolone



Phenyl methyl pyrazolone

whilst hydrazine and phenylhydrazine yield methyl pyrazolone and phenyl methyl pyrazolone. The use of substituted acetoacetic esters increases the scope of the reaction.

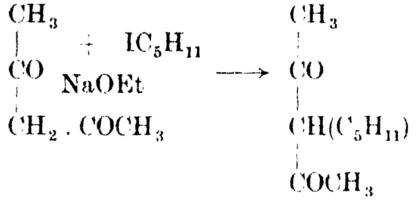
Acetone dicarboxylic ester, EtOOC . CH_2COCH_2 . COOEt. This substance is prepared by the esterification of acetone dicarboxylic acid, prepared by the action of heat on a mixture of sulphuric and citric acids. It has two fully active methylene groups and reacts accordingly. It evinces many unusual reactions, amongst which must be mentioned the fascinating synthesis of tropinone from succindialdehyde, methylamine and acetone dicarboxylic ester, which was discovered by Robinson[1] in 1917 :—



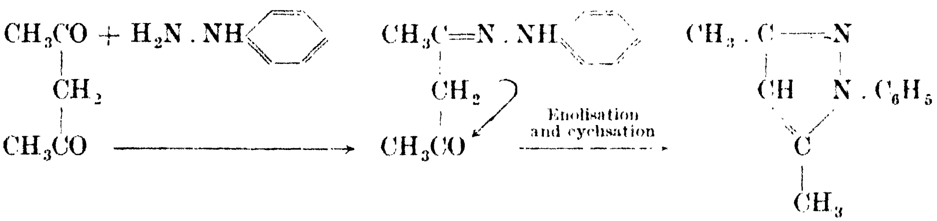
Tropinone

Diketone Syntheses

Many β-diketones, in which there is necessarily a methylene group lying between the two keto groups give reactions which are analogous to those of malonic and acetoacetic esters and their derivatives. Thus, acetyl acetone will

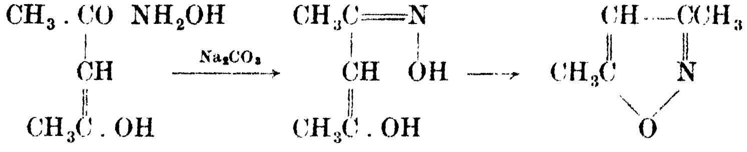


react through its sodio derivative to give the higher branched-chain, β-diketones, e.g., whilst condensation with hydrazines leads to formation of pyrazoles :—



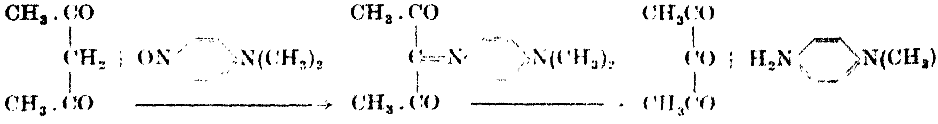
Phenyl dimethyl pyrazole

The reactions proceed equally well with hydrazine, hydroxylamine and semicarbazide giving other ring compounds. The yield of *iso*-oxazoles from acetylacetone and its homologues is almost quantitative, and the condensation takes place readily in aqueous potassium carbonate solution :—



3, 5-Dimethyl*iso*oxazole

An interesting reaction of acetyl acetone, and one which illustrates the activity of the methylene group, is its condensation with *p*-nitrosodimethylaniline and subsequent hydrolysis to pentanetrione 2, 3, 4.



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[1] R. Robinson, *J.C.S.*, 1917, **111**, 762.

APPENDIX IV

FATS, WAXES AND SOAPS

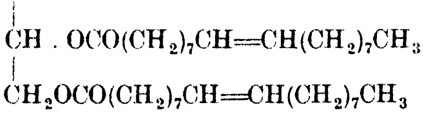
In discussing fats and waxes it is essential to clear up, at the outset, the difficulties of terminology. The whole group of substances are referred to as Lipoids, and the subdivisions set out by Hilditch (see Appendix I) will be used throughout this work. This terminology is set out below :—

	Group Title	*Lipoids*	
	SUB-GROUP I		
Contain C, H, O only	TYPE A.	Fats	Triglycerides, containing C, H and O only ; i.e., ordinary triple esters of glycerol.
	TYPE B.	Waxes	Esters of fatty acids with alcohols other than glycerol, e.g., cetyl alcohol, or cholesterol.
	SUB-GROUP II	*Lipins*	
Contain elements other than C, H, O	TYPE C.	Phosphatides	Esters of glycerol with fatty acids and containing also phosphoric acid and a nitrogenous base.
	TYPE D.	Cerebrosides	Esters of fatty acids with a carbohydrate, and containing a nitrogenous base.
	TYPE E.	—	No-generic name is applied to this series, in which there is collected together a few sulphur and nitrogen-containing lipoids excluded from the other classes.

It will be noted that no mention is made of oils in this classification, since an oil is a liquid member of Type A—a fat with a freezing point below normal temperature.

TYPE A FATS

On the whole there are more unsaturated fats than saturated, and of the former the most typical is olein, the triglyceride (482) of the oleic acid (*cis*-octadecene-9, acid)



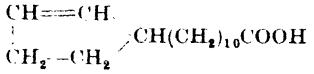
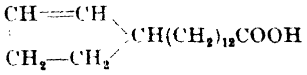
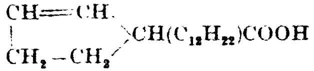
$$\begin{array}{l} CH_2OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \\ | \\ CH\ .\ OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \\ | \\ CH_2OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \end{array} \quad (482)$$

Many natural fats contain about 50–60 per cent. of oleic acid, and few have been found in which the content of this acid is below 10 per cent. It has been stated that no natural fat has been examined in which there is no oleic acid (Hilditch). Two acids appear also to be as widely distributed, but in lesser amounts ; namely linoleic acid (octadecadiene-9, 12, acid) and palmitoleic acid (zoomaric acid or hexadecene-9, acid).

After oleic acid the next most widely distributed acid is palmitic acid, hexadecane acid, $CH_3(CH_2)_{14}COOH$, whilst stearic acid, although of limited distribution, is characteristic of the main constituent of the fats of land animals. With a minor exception only even-numbered acids are found in the fats, and when one particular acid is found to preponderate, there are nearly always to

TABLE XLVIII

SOME NATURAL ALIPHATIC ACIDS

Formula	Number of d-bonds	Name	Formula
$C_{10}H_{18}O_2$	1	Decene-9, acid	$CH_2{=}CH(CH_2)_7COOH$
$C_{12}H_{22}O_2$	1	Dodecene-9, acid	$CH_3CH_2CH{=}CH(CH_2)_7COOH$
$C_{14}H_{26}O_2$	1	Tetradecene-5, acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_3COOH$
$C_{14}H_{26}O_2$	1	Tetradecene-9, acid	$CH_3(CH_2)_3CH{=}CH(CH_2)_7COOH$
$C_{16}H_{30}O_2$	1	Hexadecene-9, acid (Palmitoleic, zoomaric)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
$C_{16}H_{28}O_2$	1	(Hydnocarpic) 11-*Cyclo*pentene-2-yl-undecane acid	
$C_{18}H_{34}O_2$	1	Octadecene-9, acid (oleic)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
$C_{18}H_{34}O_2$	1	Octadecene-6, acid (Petroselinic acid)	$CH_3(CH_2)_{10}CH{=}CH(CH_2)_4COOH$
$C_{18}H_{32}O_2$	1	Octadecyne-6, acid (Tariric acid)	$CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOH$
$C_{18}H_{32}O_2$	2	Linoleic acid	$CH_3(CH_2)_4CH{=}CH\,.\,CH_2CH{=}CH(CH_2)_7COOH$
$C_{18}H_{32}O_2$	1	13-*Cyclo*penteno-2-yl-tridecane, acid (Chaulmoogric acid)	
$C_{18}H_{30}O_2$	2	13-*Cyclo*penten-2-yl, n-tridecen ?, acid	

$C_{18}H_{30}O_2$	3	Octadecatriene, 9, 12, 15 acid (Linolenic)	$CH_3CH_2CH{=}CH\,.\,CH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$
$C_{18}H_{30}O_2$	3	Octadecatriene, 6, 9, 12 acid	$CH_3(CH_2)_4CH{=}CH\,.\,CH_2\,.\,CH{=}CH\,.\,CH_2CH{=}CH(CH_2)_4COOH$
$C_{18}H_{30}O_2$	3	Octadecatriene, 9, 11, 13 acid (Elæostearic)	$CH_3(CH_2)_3CH{=}CH\,.\,CH{=}CH\,.\,CH{=}CH(CH_2)_7COOH$
$C_{18}H_{28}O_2$	4	Octadecatetrene, 9, 11, 13, 15, acid (Parinaric)	$CH_3CH_2[CH{=}CH]_4(CH_2)_7COOH$
$C_{18}H_{28}O_2$	4	Stearidonic	
$C_{18}H_{34}O_3$	1	Octadecene-9, ol 12, acid (Ricinoleic)	$CH_3(CH_2)_5CHOH\,.\,CH_2CH{=}CH(CH_2)_7COOH$
$C_{18}H_{30}O_3$	3	Octadecatriene-9, 11, 13, one-4, acid (Licanic acid)	$CH_3(CH_2)_5(CH{=}CH)_3(CH_2)_4CO(CH_2)_3COOH$
$C_{20}H_{38}O_2$	1	Eicosene-9, acid (Gadoleic)	$CH_3(CH_2)_9CH{=}CH(CH_2)_7COOH$
$C_{20}H_{32}O_2$	4	Arachidonic	
$C_{22}H_{42}O_2$	—	Docosene-11, acid (Cetoleic)	$CH_3(CH_2)_9CH{=}CH(CH_2)_9COOH$
$C_{22}H_{42}O_2$	1	Docosene-13, acid (Erucic)	$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOH$
$C_{24}H_{46}O_2$	1	Tetracosene-15, acid (Selacholeic)	$CH_3(CH_2)_7CH{=}CH(CH_2)_{13}COOH$

be found in that fat, acids with two or four less carbon atoms and probably some with two carbon atoms more. Thus, in a fat containing the ester of a C_{18} acid, there will probably also be some C_{14}, C_{16} and C_{20} acid esters.

Thus all the even-numbered aliphatic acids from C_4 to C_{26} are met with in fats as their esters, to which group must be added the odd-numbered *iso*-valeric acid whose glyceride is found in the depot fat of the dolphin. The principal unsaturated acids are listed in Table XLVIII on pages 668 and 669.

It will be observed that many of the acids of this series preserve either the $CH_3(CH_2)_7$— or the $(CH_2)_7COOH$—fragment of oleic acid, and most may, indeed, be said to be closely related to that acid. Hilditch has pointed out that the component acids of the depot (i.e., reserve or non-functional) fats of various animals tend to sort themselves into groups according to the biological origin of the animals and cites the following figures :—

	Component Acids (Percentage) of Various Animal Depot Fats				
	Saturated			Unsaturated	
	Palmitic	C_{16}	C_{18}	C_{20}	C_{22}
Fish (fresh-water)	13–15	18–20	40–45	12	0–5
Marine fish	12–15	15–18	27–30	20–25	8–12
Whales	12–15	15–18	35–40	15–20	5–10
Frog	11	15	52	15	
Tortoise	14	9	65	7	
Lizard	18	10	56	5	
Hen	25–26	6–7	60	0·5–1	
Rat	24–28	7–8	60	0·3–0·5	
Pig	25–29	2–3	50–65	0·3–1	
Ox	27–30	2–3	40–50	0·2–0·5	

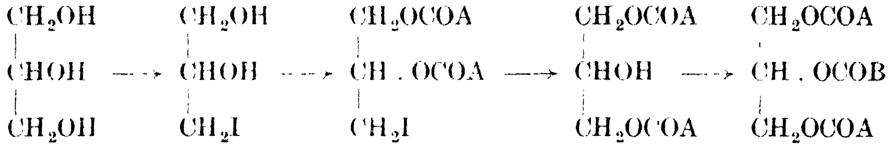
Again, the conception of structure in fats must not be regarded as constant for any species ; fats taken from plants and animals at various stages in their growth and development do not, of necessity, contain the same proportions of the various glycerides, and may vary from season to season. As an instance one may cite the differences (which are instantly revealed by analysis) in the composition of olive oil harvested at the same stages in the growth of the same trees, but in ' hot ' and ' cold ' seasons. Thus, the composition of a fat is a function of the biological history of the plant or animal and is not constant.

Further, the glycerides occurring naturally are, to a large extent, heterogeneous, and it is only rarely that the simple triglycerides are found. It will be observed that if there are three main constituent fatty acids in a fat there are eighteen possible glycerides :—

A	A	B	B	B	B
A	B	A	A	B	B
A	A	A	B	A	B
	A	C	C	C	C
	C	A	A	C	C
	A	A	C	A	C
	B	C	C	C	
	C	B	B	C	
	B	B	C	B	
	A	B	B		
	B	A	C		
	C	C	A		

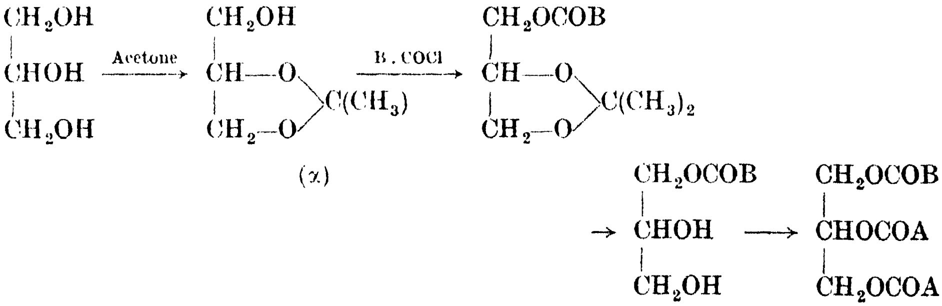
In natural fats the most complex distribution among the central section of the Group above is commonly met with, and it may be added that there is no simple way of predicting the composition a given glyceride may take. Thus, within, say, a composition of 40 per cent. palmitic, 30 per cent. oleic, and 30 per cent. stearic, there is an infinite variety of glyceride mixtures which can arise. One or two exceptions to this general rule are met with ; in seed fats the nutmeg has a fat which is very largely the simple trimyristin, and the laurel species, *Neolitsea involucrata* is largely composed of simple tripalmitin.

It will be seen that as a preliminary to the study of fats it is necessary to have exact data on the various isomeric glycerides. To accomplish this a vast amount of work has already been carried out by King and his co-workers, and much data has been collected. King has used the two methods outlined in the formulæ below :—



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2I \end{array} \longrightarrow \begin{array}{l} CH_2OCOA \\ | \\ CH\,.\,OCOA \\ | \\ CH_2I \end{array} \longrightarrow \begin{array}{l} CH_2OCOA \\ | \\ CHOH \\ | \\ CH_2OCOA \end{array} \longrightarrow \begin{array}{l} CH_2OCOA \\ | \\ CH\,.\,OCOB \\ | \\ CH_2OCOA \end{array}$$

It will be noted that although these steps are carried out by orthodox means, *e.g.*, the acid chlorides A . COCl and B . COCl are used for introduction of the acyl groups, isomerisation takes place and the final compound has the symmetrical structure. This is confirmed by using the acetone compound of glycerol which has undoubtedly, the formula (α) and by the stages indicated the isomeric and asymmetrical mixed triglyceride is obtained :—



The whole situation in respect of these triglycerides is complicated by the fact that there are three physical solid modifications of each, the stable β- form, an unstable α- form and a third form which is non-crystalline. It is essential that any comparison made on data from two glycerides should be derived from their corresponding forms. The following figures show the physical data obtained on some simple triglycerides

	Transition point of glass form	M.p. α	β
C_{10}	− 15°	18°	31·5°
C_{12}	+ 15°	35°	46·4°
C_{14}	33°	46·5°	57°
C_{16}	45°	56°	65·5°
C_{18}	54·5°	65°	71·5°

The most satisfactory data obtained were those of the long X-ray spacings, which assist considerably in the recognition of the various glycerides.

In the table below are shown some long X-ray spacings for mixed glycerides (in the β- form) :—

TABLE XLIX

A	B	Structure			
		A B A	B A B	A A B	B B A
Lauryl	Capryl	30·0	29·0	31·8	28·4
Myristyl	Lauryl	34·7	33·6	36·5	33·0
Palmityl	Myristyl	39·0	38·1	41·5	37·7
Stearyl	Palmityl	44·2	43·2	46·5	42·5
Myristyl	Capryl	52·5	46·5	35·2	47·5
Palmityl	Lauryl	59·0	35·5	39·8	54·6
Stearyl	Myristyl	65·8	40·0	45·0	61·4

The Figures are in Ångström units

From the table it will be seen that there is a specific long spacing for each glyceride which materially assists in the identification.

WAXES

It might appear from a casual inspection of the literature that the waxes presented a comparatively simple problem of structure, compared with that of the fats, since they are largely simple esters of primary long-chain alcohols with primary long-chain acids. Such is not the case ; the older literature makes continual reference to, and expresses, the structure of waxes in terms of ' ceryl ', ' melissyl ' and ' miricyl ' alcohols, and of ' arachidic ', ' lignoceric ', ' cerotic ' and ' montanic ' acids ; and of many more with names, e.g., ' pisangceric ', which are a combination of the name of the source and ' ceric '. Some of these compounds have no real existence as chemical individuals and should be struck out from the literature.

The painstaking and exhaustive researches of Chibnall,[1] Piper and others of the same school, have clearly demonstrated that what have for generations been referred to as the ' acid ' and ' alcohol ' fractions of waxes are most complex mixtures of even-numbered acids and alcohols, with an occasional keto- or secondary alcohol, together with odd-numbered paraffins. The elucidation of the nature of these acids, alcohols and esters is a triumphant application of X-ray analysis, and shows that the waxes, like the fats, are a complex mixture of esters. Some of the final conclusions concerning the nature of these compounds is shown in Table L. This is, perhaps, an appropriate point to mention that many fats from the fish livers contain glyceryl ethers with alcohols as delineated below :—

Chimyl alcohol.	$CH_3(CH_2)_{15}OCH_2CH(OH)CH_2OH$
Batyl alcohol.	$CH_3(CH_2)_{17}OCH_2 . OH(OH)CH_2OH$
Selachyl alcohol.	$CH_3(CH_2)_7CH{=}CH(CH_2)_8OCH_2 . CHOH . CH_2OH$

Various interesting speculations have been made as to the biochemical significance of these compounds, but their rôle is not clear.

---

[1] Chibnall *et al.*, *Biochem. J.*, 1934, **28**, 2189. This paper contains a useful summary of this work.

TABLE L—THE COMPONENTS OF SOME WAXES

Wax	Source	Alcoholic components	Acidic components
Apple wax	Skin of apple	Primary alcohols, C_{26}, C_{28}, C_{30}. Sec. alcohol *d*-*n*-nonacosan-10 ol. Paraffins C_{27} and C_{29}	Normal acids C_{26}, C_{28}, C_{30} and C_{32}
Beeswax	Common hive bee (*Apis mellifica*)	C_{24}-C_{34} even-numbered alcohols. The paraffins C_{25}, C_{27}, C_{29} and C_{31}	The even-numbered acids C_{24}-C_{34}
Candelilla	Euphorbiacae (mainly *Pedilanthus paronis*)	35–40 % of both C_{30} and C_{32}; and 10–15 % of both C_{28} and C_{34}. Remainder. C_{31} hydrocarbon	Roughly equimolar acids C_{30} – C_{32} – C_{34}
Carnauba	As a coating to palm leaves; the palm is *Copernica cerifera*	Primary even alcohols C_{26} and C_{34}. Also *n*-Heptacosane	The acids C_{30}, C_{32}, C_{34}
Chinese Insect wax	*Coccus ceriferus*	The so-called 'ceryl alcohol' is a mixture of approx. 40 % C_{26} + 40 % C_{28} – 20 % C_{30}	The so-called 'cerotic acid' is a mixture of C_{26}, C_{28} and C_{30} acids
Cochineal	Cochineal insect (*Coccus cacti*)	15-Keto-*n*-tetratriacontanol $CH_3(CH_2)_{18}CO(CH_2)_{13}CH_2OH$	*n*-Triacontanoic acid $CH_{13}(CH_2)_{28}COOH$. 13-Keto-*n*-dotriacontanoic acid
Cocksfoot grass	—	*n*-Hexacosanol, $C_6H_{53}OH$ (almost alone, of the higher alcohols)	—
Cotton	*Gossypium*	All the even alcohols C_{24}-C_{34}. At least 3 paraffins	All the even acids C_{24}-C_{34}
Ghedda wax	*Apis dorsata*	Even-numbered alcohols C_{24}-C_{30}. Paraffins C_{27} and C_{31}	Even-numbered acids C_{24}-C_{34}
Psylla wax	The plant louse, *Psyall ani*	A mixture of C_{30}-C_{36} alcohols and an unidentified paraffin	The even-numbered *n*-acids, C_{30}-C_{34}
Lac	Lac insect (*Coccus lacca* Kerr *Tachardia Lacca* Kerr)	Contains (*a*) alcohol sol. fraction which is a mixture of primary alcohols C_{26}, C_{28}, C_{30}, C_{32}, (*b*) alcohol insoluble esters of the primary alcohols, C_{30}-C_{36} with the even-numbered fatty acids, C_{30}-C_{34}	
Raphia	*Raphia tuffia*, in the leaves	40 % each C_{28} + C_{30}; 20 % C_{32} alcohols	Practically no acid
Ryegrass	—	*n*-Triacontanol. *n*-Tetradecanol 8 %	—
Sperm and blubber oils	Whale	*n*-Hexadecanol 45–50 % (cetyl), *cis*-*n*-Octadecene-9, ol-1 (oleyl)	Palmitic
Spermaceti	Head of sperm-whale	*n*-Hexadecanol	Palmitic
Tobacco wax	*Nicotiana affinis*	Almost entirely paraffin, probably C_{25}, C_{27}, C_{29}	No acids
Wheat	—	*n*-Octacosanol (almost alone of the higher alcohols)	—

CHAPTER IX

TERPENES AND RELATED COMPOUNDS

> " And because the breath of flowers is far sweeter in the air, where it comes and goes, like the warbling of music, than in the hand, therefore nothing is more fit for that delight, than to know what be the flowers and plants that do best perfume the air."
>
> —BACON (" Of Gardens ").

The plant kingdom yields a vast number of pleasantly smelling oils and solids which by virtue of their odour have attracted attention from the earliest times. Some such as coumarin, vanillin, eugenol, and apiol, are purely aromatic in the chemical sense, and their constitution was comparatively easily ascertained ; others, often described as the " volatile " or " ethereal " oils, proved more difficult to investigate, and only in the later decades of the last century and the first twenty years of the present century have their structures been established.

Some aliphatic substances of powerful odour, which are not apparently related to the terpene family, have been isolated from plants. Thus, from *Eryngium foetidum* Koolhaas[1] isolated 2–dodecenal, and Ruzicka[2] showed that violet leaves owe their perfume to 2, 6-nonadienal.

$CH_3[CH_2]_8CH{=}CH\ .\ CHO$ 2–Dodecenal

$CH_3CH_2\ .\ CH{=}CH[CH_2]_2CH{=}CH\ .\ CHO$ 2, 6–Nonadienal

The following classification of the terpene family is conveniently based on the number of carbon atoms of the compounds :—

C_5	Hemiterpenes.
C_{10}	True terpenes.
C_{15}	Sesquiterpenes.
C_{20}, C_{30}, C_{40} and higher	Polyterpenes.

Of the so-called hemiterpenes, only isoprene is of importance but there are several hundred true terpenes, subdivided for convenience into the classes :—

(1) Olefinic terpenes.
(2) Monocyclic terpenes.
(3) Dicyclic terpenes.

All, with one or two exceptions, are related structurally to *p*- and *m*-cymene, the majority to the former ; (1) represents a typical olefinic terpene structure ; (2) a simple monocyclic terpene. The dicyclic terpenes are derived from the four structures (3) to (6) sabinane, carane, pinane, and camphane.

Sesquiterpenes may be subdivided into groups similar to those of the ordinary terpenes (1) olefinic, (2) monocyclic, (3) dicyclic, whilst, in addition, there are some members of a fourth, or tricyclic class. A typical olefinic sesquiterpene skeleton is shown in (7), and one form of monocyclic sesquiterpene in (8); dicyclic sesquiterpene skeletons are shown below :—

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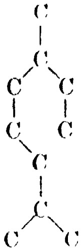
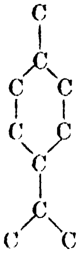
[1] Koolhaas, *Rec. Trav. Chim.*, 1932, **51**, 460.
[2] Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1592.


(1)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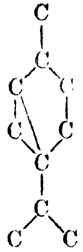
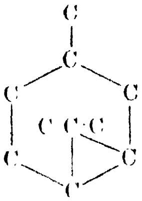

(3)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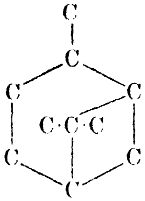
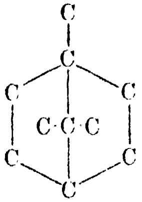

(5)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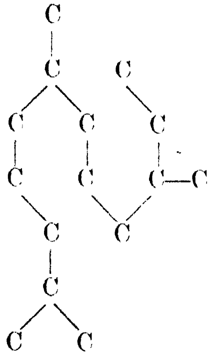
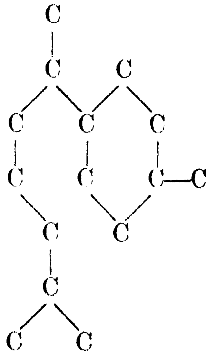
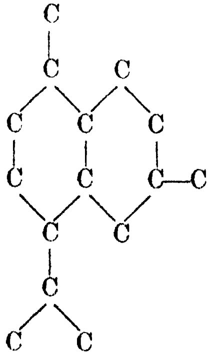
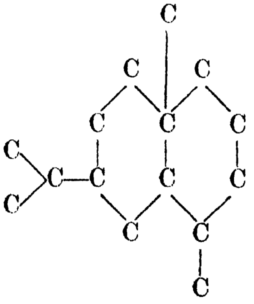

(7)


(8)


Cadalene skeleton

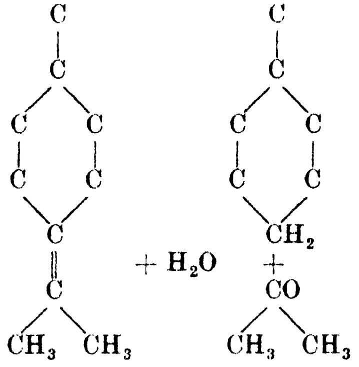

Selinene skeleton

Polyterpenes are represented naturally by the diterpenes, derived from $C_{20}H_{32}$, such as colophene and copaitene; triterpenes by the amyrilenes, and in another sense, the rubbers and synthetic rubbers may be considered to be related to the polyterpenes.

GENERAL PROPERTIES

In general, terpenes are characterised by the ease with which they are converted from one structure to another by simple reagents ; the section below entitled " Cyclisation of Olefinic Terpenes " illustrates this point. Such ease of transformation has made the elucidation of structure more difficult.

Since most terpenes are unsaturated, a study of their structure is bound up with breakdown at the double bond. Oxidative attack, using progressively stronger reagents, has proved a valuable method (*vide* Terpineol and Pinene), and in some cases the use of ozone and benzoyl peroxide has proved useful. Where a double bond lies between a cyclic structure and an *iso*-propylidene group, as in (9), hydrolytic fission to give acetone and a cyclohexane derivative has proved a valuable method of elucidating structure. Addition compounds with nitrosyl chloride, halogen acids, and occasionally the halogens themselves, are capable of affording much information.

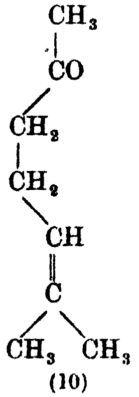


(9)

The chemistry of the " hemi-terpene " isoprene has already been discussed (p. 97 ff.) ; further comment will be deferred to the end of this section, where it is better considered in relation to the phytochemistry of the terpenes as a whole.

THE OLEFINIC TERPENES

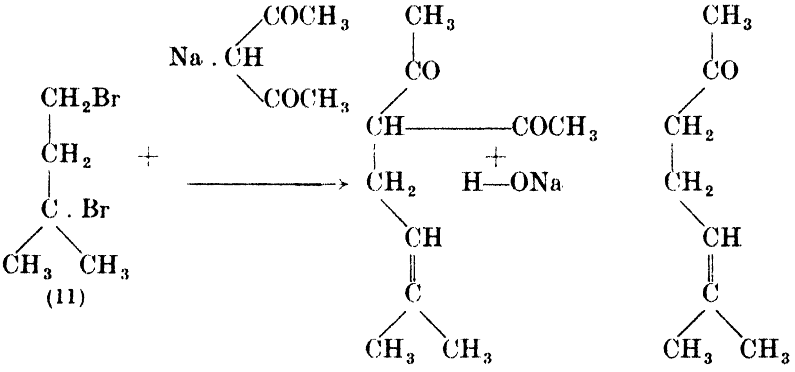
There is a relation between the olefinic terpenes and the higher plant ketones and hydrocarbons. Both methyl nonyl ketone (methyldecanone) and methyl heptanone occur in oil of rue (*Ruta graveolens*), but the most important



(10)

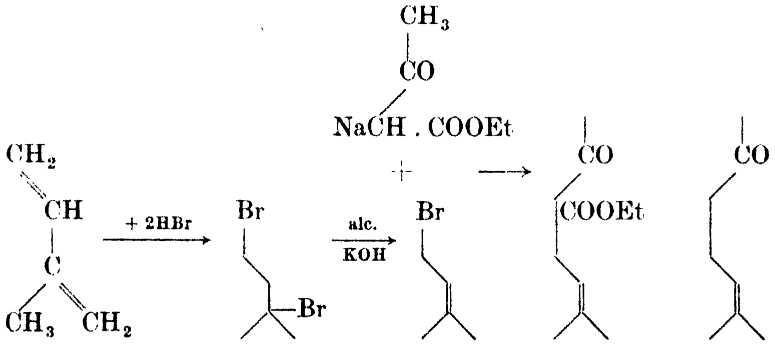
naturally occurring ketone of this group is 2-methylheptene-2, one-6 (" methyl heptenone ") (10).

Methylheptenone is a convenient starting-point for a study of the chemistry of the olefinic terpenes. It is a liquid of pleasant floral odour, b. 171° ; it occurs only to a limited extent in natural oils (linaloe, palmarosa, and lemongrass), but has been synthesised. If 3-methyl-1, 3-dibromobutane (11) is allowed to react with the sodio derivative of acetylacetone, only the terminal bromine atom reacts normally, the more labile bromine of the tertiary carbon atom being split off with hydrogen from the adjacent atom to give a double bond, as in (12). The compound so formed is decomposed by 40 per cent. sodium hydroxide solution to methyl heptenone and sodium acetate.



(11) (12) (13)

A more rapid and economical synthesis of methylheptenone is achieved as follows :—



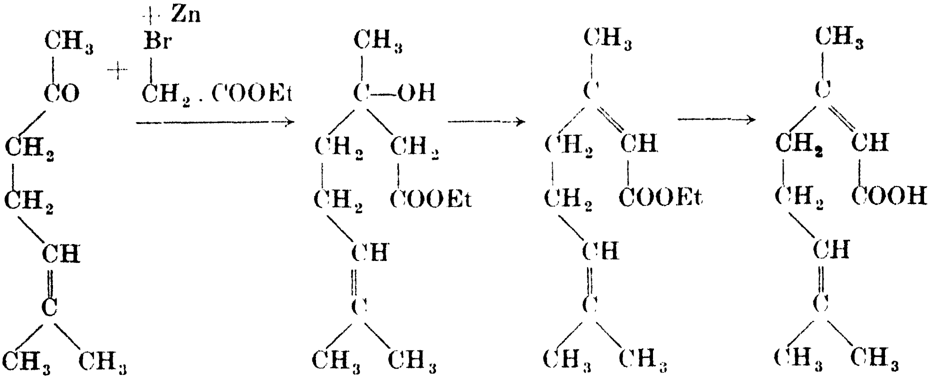
(14) (15) (16) (17) (18)

Isoprene (14) is allowed to react with two molecular proportions of hydrogen bromide to give 3-methyl-1, 3 dibromo-butane (15) ; this loses one molecule of hydrogen bromide when warmed with dilute alcoholic potash to provide 3-methyl-1-bromobutene-2 (16), which furnishes the ester (17) on treatment with sodio-acetoacetic ester. Hydrolysis of this ester to the acid results also in the loss of carbon dioxide, giving methylheptenone (18).

The relation of methyl heptenone[1] to the olefinic terpenes lies through geranic acid which can be converted to rhodinol, rhodinal, citral, citronellol, geraniol, nerol and linalool. Conversion of methylheptenone to geranic acid is a good example of the Reformatski reaction. The ketone is allowed to react with bromoacetic ester in the presence of zinc, giving (19):—

---

[1] Experiments with methylheptenone led Grignard to discover what are now termed " Grignard " reagents ; although V. Grignard (a student of Barbier's) did much experimental work on their development, Barbier should share the initial credit.

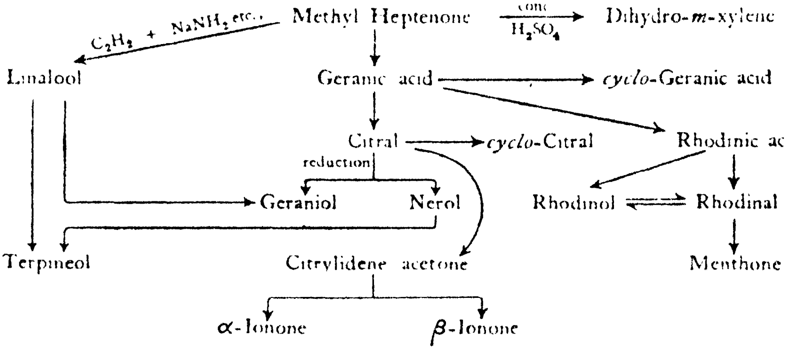


(19) (20)

which may be dehydrated by boiling acetic acid to geranic ester, and at the same time hydrolysed to the free acid (20).

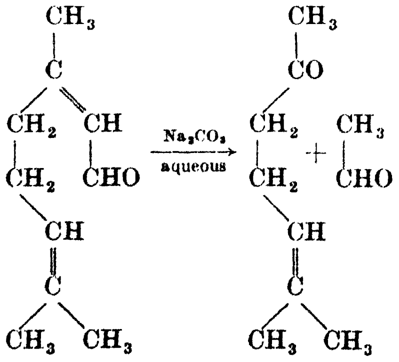
The generic relationships of this family of compounds is shown in Table I.

TABLE I



CITRAL

Citral, $C_{10}H_{16}O$, occurring in oils of verbena, lemon and orange to a limited extent, and to 70–80 per cent. in oil of lemon-grass (*Cymbopogon* species) is converted[1] by heating with aqueous sodium carbonate into methyl heptenone and acetaldehyde (22):—



(21) (22)

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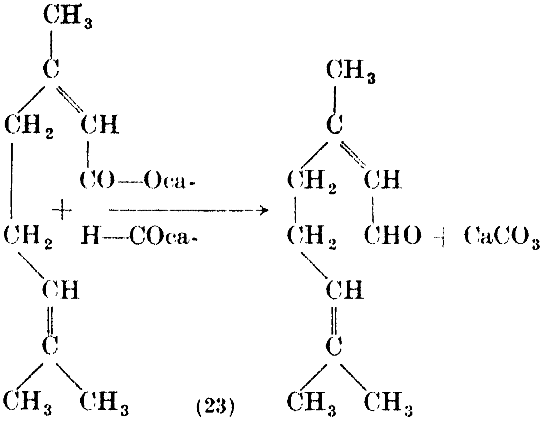
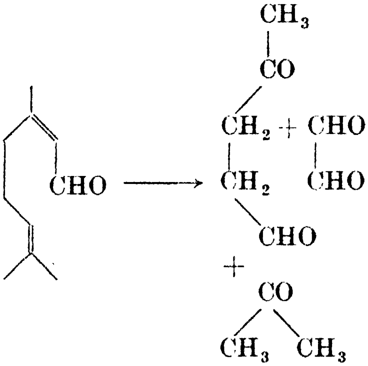
[1] Verley, *Bull. Soc. Chim.*, 1897 [iii], **17**, 175.

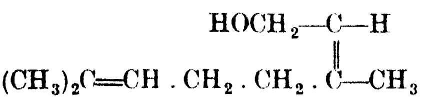
which, bearing in mind that citral is an aldehyde, gives an *a priori* case for the formula (21). • When calcium geranate[1] and formate are distilled together, citral (23), is obtained, thus confirming the structure. This is even more completely confirmed by the hydrolysis of citral diozonide which yields a molecule each of glyoxal, levulic aldehyde (pentanal-one-4) and acetone, thus :—



(23)

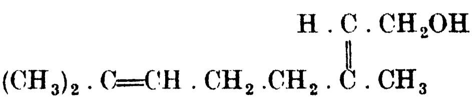


Reduced in dilute alcoholic acetic acid by sodium amalgam, nerol and geraniol, the corresponding alcohols, are both obtained. These exhibit geometrical isomerism thus :—



$$\begin{array}{l}\qquad\qquad\qquad\quad HOCH_2{-}C{-}H\\ \qquad\qquad\qquad\qquad\qquad\ \ \|\\ (CH_3)_2C{=}CH\,.\,CH_2\,.\,CH_2\,.\,C{-}CH_3\end{array}$$

(24)



$$\begin{array}{r}H\,.\,C\,.\,CH_2OH\\ \|\qquad\quad\\ (CH_3)_2\,.\,C{=}CH\,.\,CH_2\,.CH_2\,.\,C\,.\,CH_3\end{array}$$

(25)

The question arises as to which formula represents nerol and which geraniol. In a subsequent section dealing with cyclisation of olefinic terpenes, it is pointed out that both nerol and geraniol give terpineol on warming with acetic acid containing 2 per cent. of sulphuric acid. With nerol, the rate of formation of terpineol is nearly ten times that with geraniol, from which it is argued that nerol must have the structure (24), since the groups are more favourably placed in this structure for ring closure ; formula (25) will, therefore, represent geraniol.

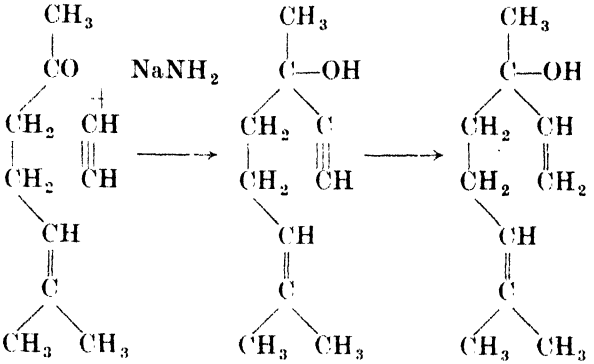
Further, citral itself has been shown to be a mixture of two geometrical isomerides corresponding to nerol and geraniol.

---

[1] In formulæ where the calcium salts of acids are involved, the " ca- " implies that a second radicle is attached to the calcium, which, owing to printing difficulties, has been omitted from the formulæ.

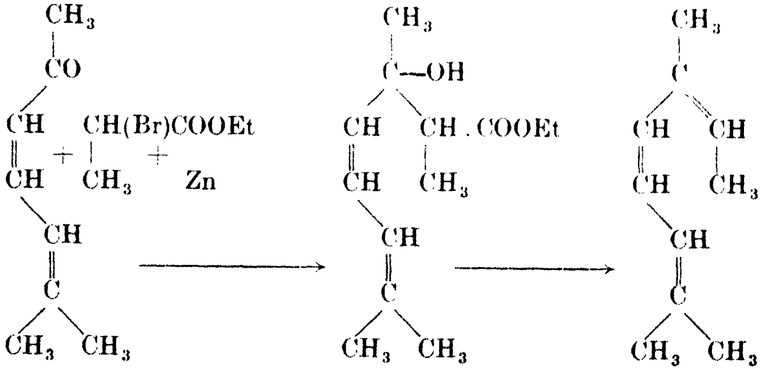
LINALOOL

Linalool is a colourless liquid, b. 199°, found in oils of linaloe and coriander; it has a delightful odour, resembling lily of the valley. Methyl heptenone was converted by Ruzicka and Fornasir[1] into linalool (28) by the sodamide and acetylene method (26):—

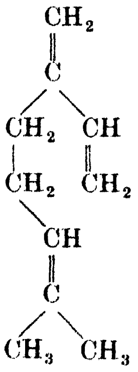


(26) (27) (28)

dehydrolinalool being first formed (27). Reduction of dehydrolinalool to linalool with sodium in moist ether finally established the structure. Esters of linalool, especially linalyl acetate, are widely distributed as natural perfumes in sage, clary, lavender, coriander and many others. An *iso*-linalool is stated to be obtained by the action of alkalies on tribromohydrogeraniol.



(29) (30) (31)



(32)

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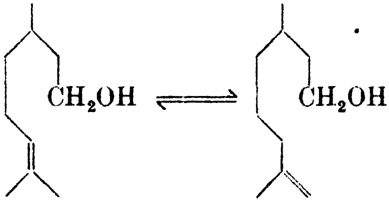
[1] Ruzicka and Fornasir, *H. Ch. Acta*, 1919, **2**, 182

The naturally occurring *allo*-ocimene is related to this series and has some points of interest; it is obtained by isomerisation of the unstable natural hydrocarbon ocimene; by the pyrolysis of pinene (25 per cent. yield; glass at 350°), and by synthesis from 2-methyl heptadiene-2, 4-one-6 (29), and α-bromopropionic ester in the presence of zinc, the hydroxy ester (30) being converted to *allo*-ocimene (31) by hydrolysis to the free acid, which, on heating, loses carbon dioxide and water.

The isomeric myrcene from oil of bay is the only other important open chain hydrocarbon of the terpene group. Myrcene (32) differs from ocimene only in the position of the double bonds.

RHODINOL AND CITRONELLOL

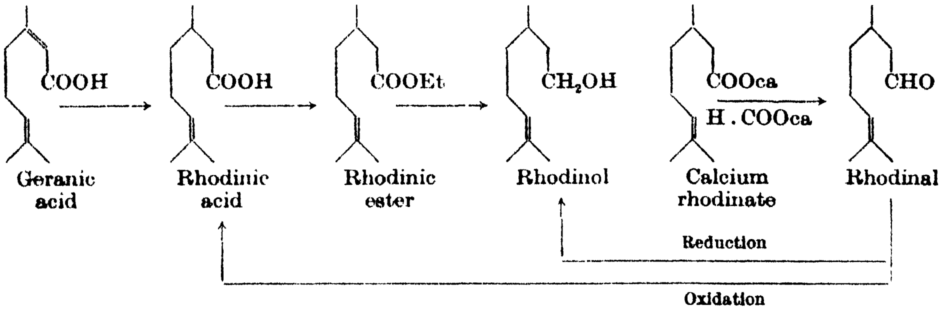
It appears that the compounds usually known as rhodinol and citronellol are largely mixtures of the two isomeric alcohols :—



I II

Structure I is rhodinol, and II is citronellol, and this distinction is maintained for those natural and synthetic preparations in which the appropriate structure predominates.

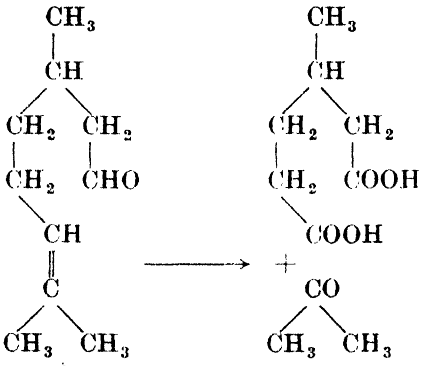
Geranic acid is reduced readily by sodium and amyl alcohol to dihydrogeranic acid, the double bond adjacent to the carboxyl group being reduced preferentially. This acid is often known as rhodinic acid, and is also obtained by the oxidation of rhodinol or rhodinal. It may be converted by reduction of its ester with sodium and ethanol to rhodinol whilst rhodinal may be obtained (cf. citral) by distilling together calcium rhodinate and formate. These changes are represented thus :—



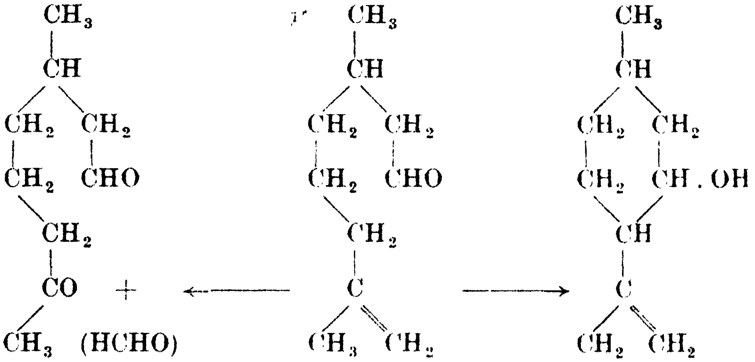
CITRONELLAL AND RHODINAL

Confusion similar to that discussed with the corresponding alcohols, exists with the aldehydes citronellal and rhodinal and most natural or synthetic products to which these names are attached prove to be mixtures of the two isomers.

Citronellal is the main odorous constituent of citronella oil, and also occurs in lemongrass oil. Considerable confusion was caused in the early investigations on citronellal, $C_{10}H_{18}O$, by its oxidation in aqueous solution to acetone and β-methyl adipic acid (34), from which Tiemann and his co-workers deduced that it must have the structure (33) now accorded to rhodinal :—


(33) (34)

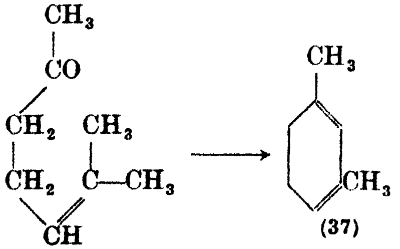
Harries and others ascertained that oxidation of the dimethyl acetal of citronellal gave the keto-aldehyde (35), thus pointing to the structure (36) for


(35) (36) (36a)

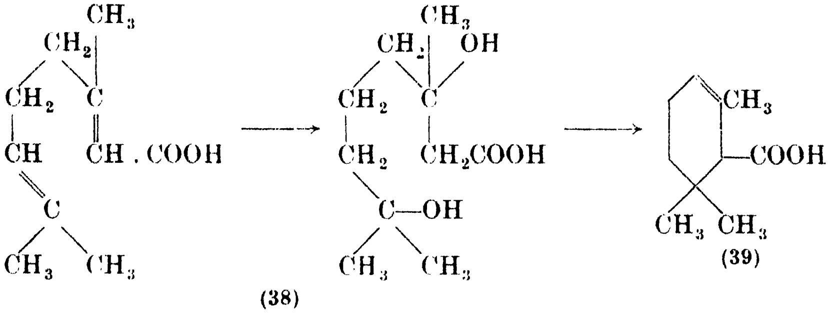
citronellal. The final proof lies in the conversion of citronellal into *iso*-pulegol and (36*a*), the structure of which may be verified in other ways (see p. 698).

CYCLISATION OF CITRAL SERIES

There is a strong tendency on the part of many members of this series to form ring compounds. With methylheptenone, 75 per cent. sulphuric acid induces dehydration to dihydro-*m*-xylene (37) :—

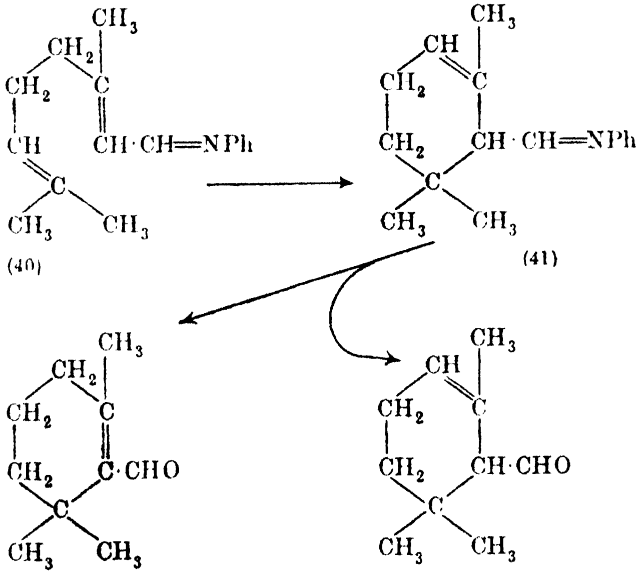

(37)

On the other hand, ring closure of geranic acid takes place through the central carbon of the *iso*propylidene section :—



(38) (39)

α-*cyclo*geranic acid (39) being formed, presumably through the intermediate (38) or a succession of similar compounds. An analogous transformation is given by citral itself, providing its aldehyde group has been made unreactive ; thus, citrylidene aniline (40) is transformed into α-*cyclo*citrylidine aniline (41), which



(40) (41)

(42) α-form β-form (43)

CYCLOCITRAL

gives *cyclo*citral on hydrolysis, as a mixture of the two forms (α- and β-) (42) and (43), the β-form being analogous to β-*cyclo*geranic acid.

This reaction may be extended to derivatives of citral ; for instance, when citral is condensed with acetone in the presence of baryta, a citrylidene acetone (44) is obtained, more usually called pseudo-ionone. Cyclisation of citrylidene acetone by sulphuric acid takes place in the same manner as with citrylidene aniline. The products α- and β-ionone (45) and (46) possess an odour of violets and are utilised in compounding artificial violet perfumes. The formation of the ionones is undoubtedly due to a sequence of hydration and dehydration reactions similar to those mentioned under *cyclo*geranic acid. The characteristic ionone ring is met with in the structure of vitamin A, for the synthesis, of which β-ionone is the raw material. Ruzicka[1] has shown that irone, $C_{14}H_{22}O$, the characteristic violet-smelling ketone of natural occurrence in orris root (*Iris* species), is an ionone derivative (47); on oxidation it yields the corresponding trimethyl pimelic acid (48).

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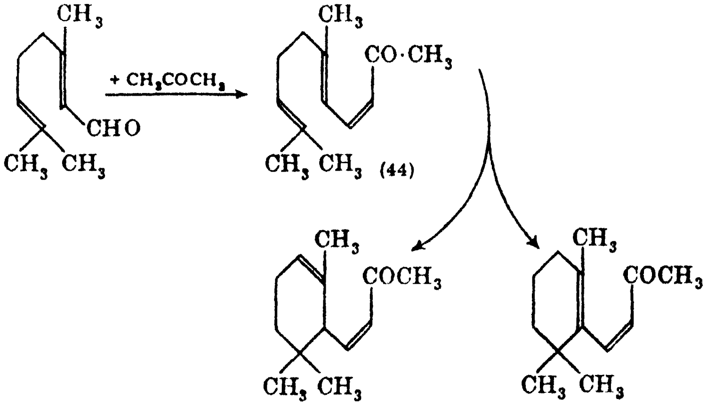
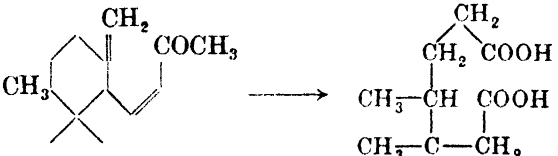
[1] Ruzicka, Seidel and Schinz, *Helv. Chim. Acta*, 1933, **16**, 1143.



α-IONONE
(45)

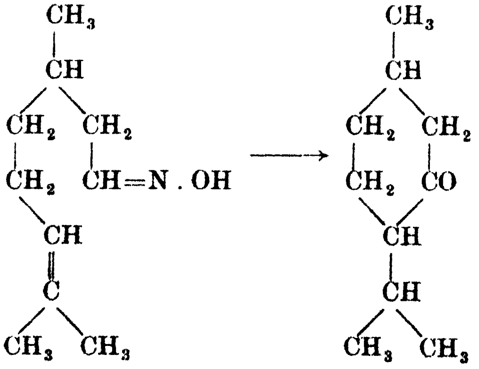
β-IONONE
(46)



γ-IRONE
(47)

(48)

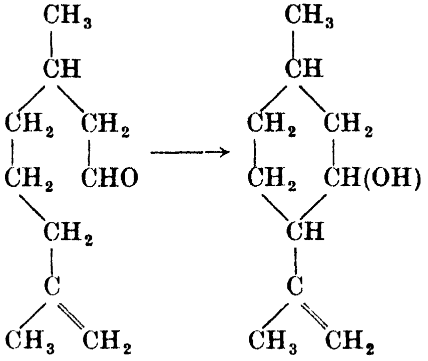
Cyclisation of many olefinic terpenes gives true monocyclic terpenes, these reactions serving to indicate the close relation between the two groups. Thus, rhodinal oxime (49) is converted by acetic anhydride into menthone (50).



(49)

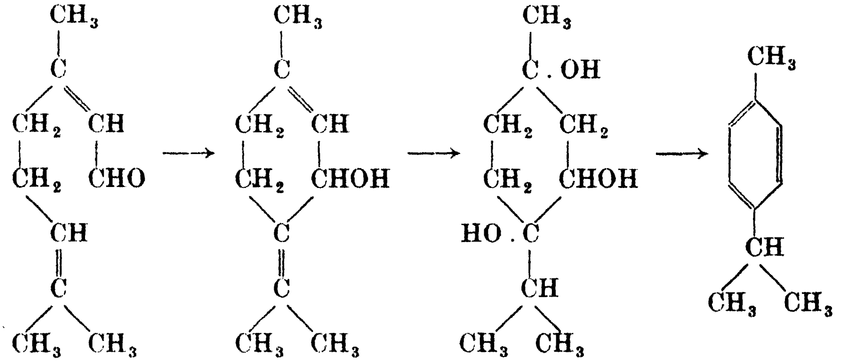
(50)

Citronellal (51) is converted by the same reagent to *iso*pulegol (52).



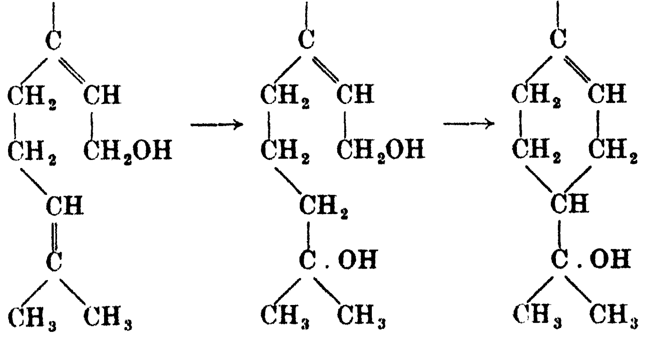
(51) (52)

Both changes involve wandering of a single hydrogen atom, but in opposite directions. Citral (53) under the same conditions, gives a substance (54) analogous to *iso*pulegol, but which is converted by prolonged treatment with acetic acid to *p*-cymene (56), presumably through the trihydroxy derivative (55).



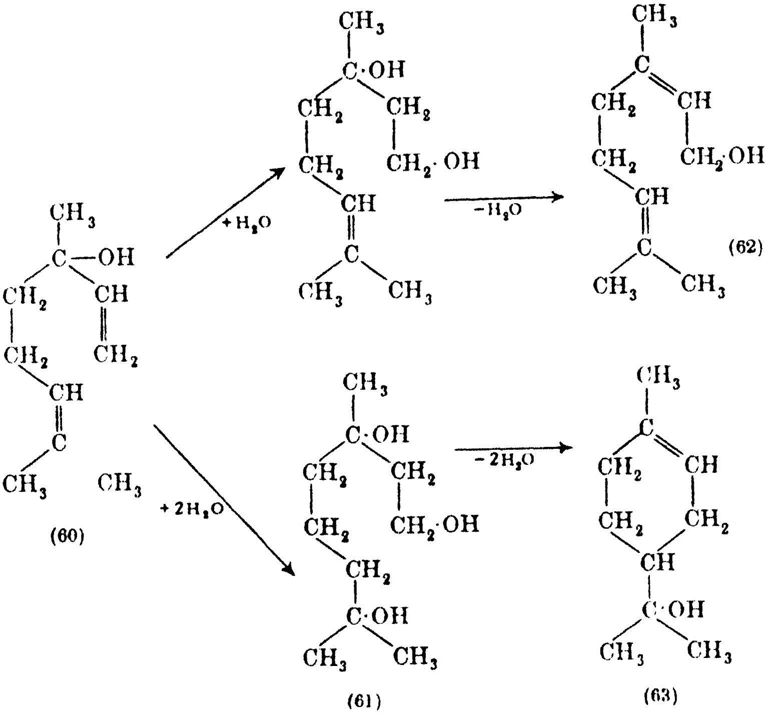
(53) (54) (55) (56)

Geraniol and nerol (57) are converted by acetic acid containing 2 per cent. of sulphuric acid to terpineol (59); it is not clear whether ring formation and the addition of water are sequential or simultaneous, but the formation of an intermediate glycol (58) has been suggested and is probable.

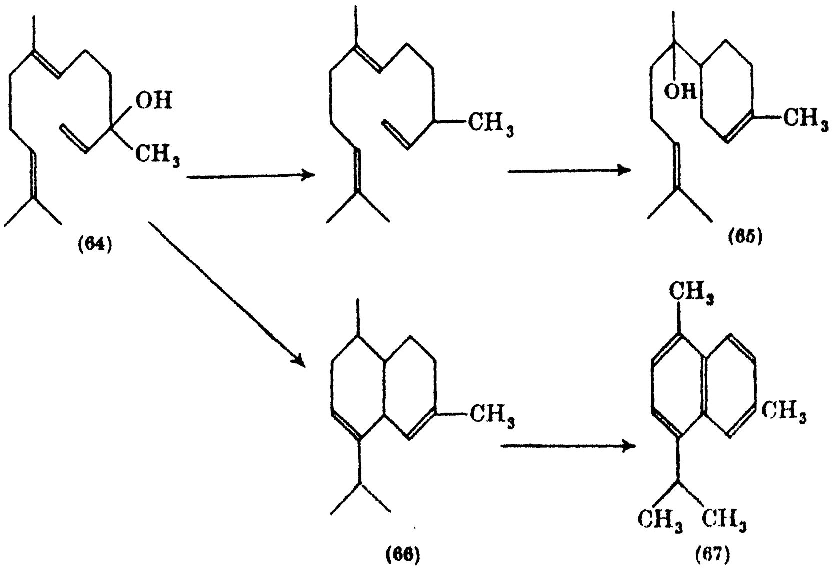


(57) (58) (59)

Linalool presents a somewhat more difficult problem; DL-linalool is converted by acetic anhydride into a mixture of nerol and geraniol (62); L-linalool (60) is stated to give an optically active terpineol (63) in addition. If a series of hydrated intermediates is postulated (61), there seems no reason why the activity of the carbon atom of L-linalool should result in an active terpineol in which the asymmetric carbon atom is at the other end of the molecule.



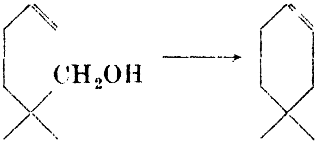
Similar cyclisations take place amongst open-chain sesquiterpenes; nerolidol



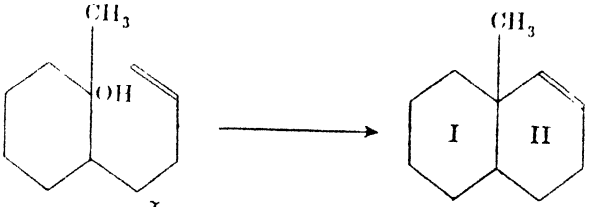
(64), for example, readily yields (probably through farnesene), the monocyclic sesquiterpene α-bisabolol (65).

On the other hand, nerolidol (64) is cyclised by boiling formic acid to a hexahydrocadalene (66) which, in turn, is dehydrogenated readily by sulphur or selenium to cadalene itself (67).

This type of reaction is of fundamental importance in building up ring systems akin to those found in the natural sterols. The cyclisation of dimethylhexenol to dimethyl*cyclo*hexene (69) was extended by Linstead and his co-workers to the formation of 9-methyl derivatives of octalin, thus obtaining a hydrocarbon having the I and II rings of the sterol structure.



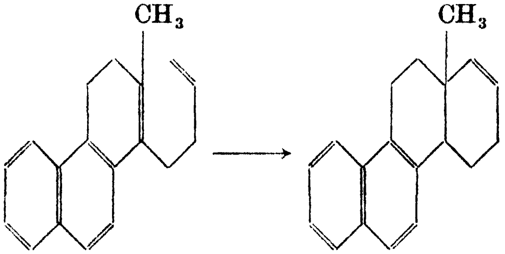
(68) (69)



1-Methyl-2-Δ^{γ}-butenyl*cyclo*hexanol

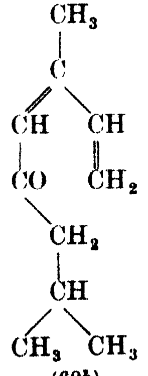
9-Methyl-Δ^1-octalin

This is carried even further by Cook and others, who have cyclised 2-methyl-1-Δ^{γ}-butenyl-3, 4-dihydrophenanthrene (69*a*) to a chrysene derivative :—

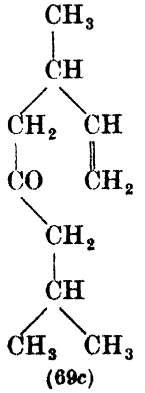


(69*a*)

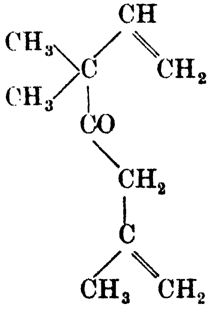
Mention should also be made of the interesting structures of tagetone (69*b*) and its dihydro derivative (69*c*) and of the ketone (69*d*) isolated from *Artemisia* :



(69*b*)



(69*c*)

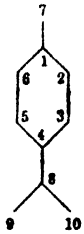


(69*d*)

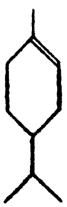
the former is notable for a carbonyl group in an unusual position, and tagetone itself (from *Tagetes Glandulifera*) is unusual in having a conjugated diene system. The ketone from *Artemisia* is one of the few naturally occurring substances showing a *neo*-carbon atom.

THE MONOCYCLIC TERPENES

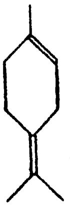
Some anomalies, peculiar to the class, are met with in the nomenclature of cyclic terpenes. Wagner regarded them as derived from the fully saturated hydrocarbon $C_{10}H_{20}$, 1-methyl-4-*iso*-propyl*cyclo*hexane, which he termed



(70)



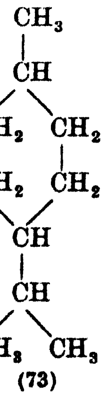
(71)



(72)

' menthane " and numbered as in (70). Thus, (71) would be called Δ^1-menthene and (72) $\Delta^{1, 4\text{-}8}$ menthadiene. Baeyer used the terms, terpane, terpene and terpadiene, etc. ; whilst there is no particular reason why these methods should be used in preference to more systematic nomenclature derived from 1-methyl-4-*iso*propyl*cyclo*hexane, custom has in many cases established such usage.

It is proposed to introduce this group of compounds by consideration of the " key-substance " α-terpineol, a pleasant-smelling liquid of comparatively limited natural occurrence in oils of marjoram, cardamom and cajuput, but which is frequently obtained from other terpenes by the action of mild hydrolytic agents. The empirical formula $C_{10}H_{18}O$, and the molecular weight 154, indicate that α-terpineol is probably a derivative of hexahydrocymene, confirmation being readily obtained since *p*-cymene is formed when terpineol is dehydrogenated with either sulphur or selenium. The general chemical behaviour of α-terpineol shows it to be a tertiary alcohol, and the formation of a nitrosochloride indicates the presence of a single double bond. α-Terpineol



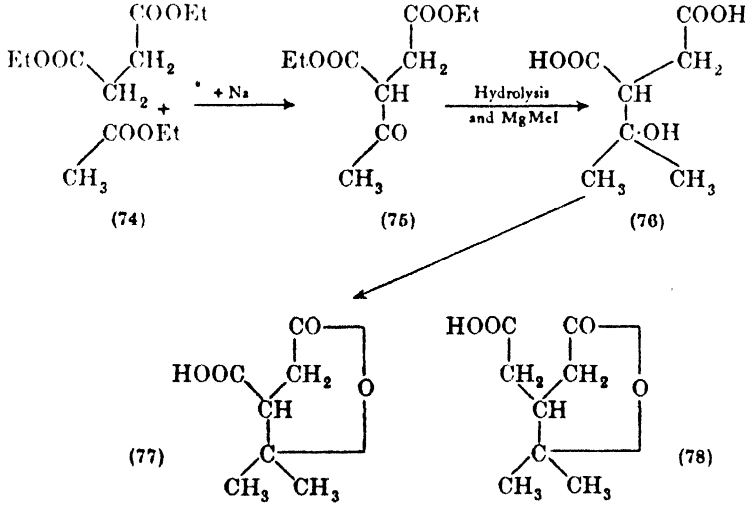
(73)

may, therefore, be regarded as hexahydro-*p*-cymene (73) into which one double bond and a hydroxyl group have to be inserted. The position of these functional groups has been ascertained by degradative oxidation. When terpineol is oxidised the following stages may be observed :—

Oxidation of Terpineol

	$C_{10}H_{18}O$	Terpineol
I	$C_{10}H_{20}O_3$	Formed by addition of the elements of hydrogen peroxide to the double bond, forming a trihydroxyhexahydrocymene.
II III	$C_{10}H_{18}O_3$ $C_{10}H_{16}O_2$	A ketone-acid (II) which loses water as soon as formed, passing into the lactone of homoterpenylic acid methylketone (III).
IV	$C_8H_{12}O_4$	When homoterpenylic acid methylketone (III) is further oxidised, it splits up into acetic acid and terpenylic acid (IV).
V	$C_7H_{10}O_4$	Terpenylic acid on further oxidation loses —CH_2 and becomes terebic acid (V), which has been synthesised.

The synthesis of terebic acid has been achieved as follows : Ethyl acetate and succinic ester (74) are condensed in the presence of sodium to give acetyl succinic ester (75). The corresponding acid, with magnesium methyl iodide, followed by hydrolysis gives the hydroxy- acid (76), which immediately cyclises to terebic acid (77).

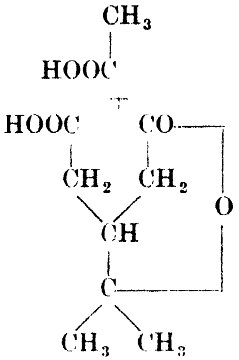


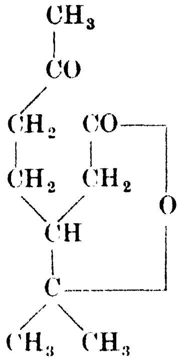
(74) (75) (76)

(77) TEREBIC ACID

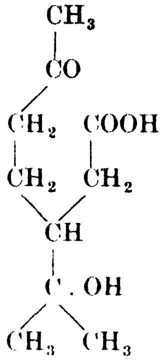
(78) TERPENYLIC ACID

In the same way terpenylic acid (78) has been synthesised from β-acetylglutaric acid. Since terpenylic and acetic acids were produced from the lactone of homoterpenylic methylketone, it is a justifiable assumption that the latter compound, and the acid from which it is derived, are formulated (79) and (80).



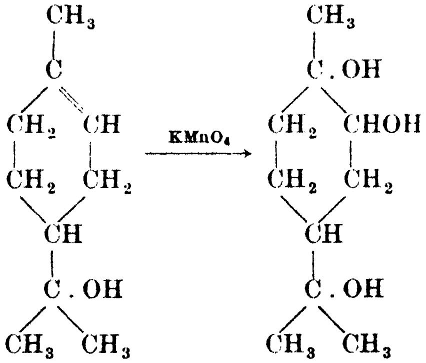


(79)



(80)

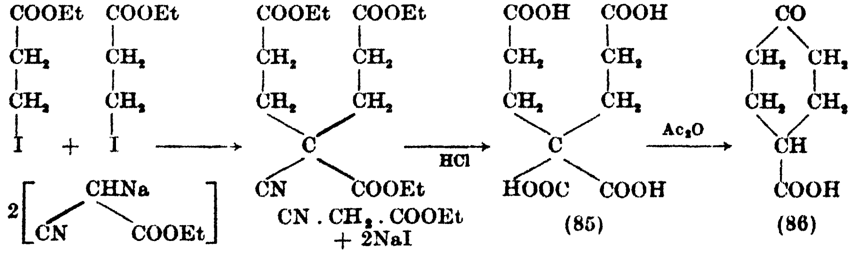
The carbonyl and carboxyl groups in (80) must indicate the site of the double bond of α-terpineol (81) and of the adjacent hydroxyl groups of trihydroxyhexahydrocymene (82) :—



α-Terpineol (81)

(82)

The synthesis of α-terpineol by W. H. Perkin, jun., in 1904[1] confirmed this structure. The sodium derivative of cyanacetic ester was allowed to react with



(83)

(84)

(85)

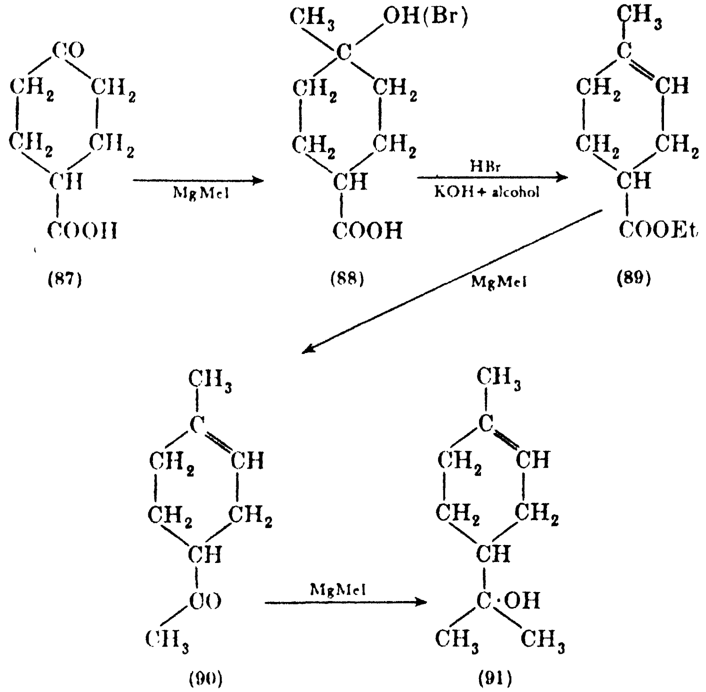
(86)

β-iodopropionic ester (83), thus producing the 3-cyanopentane-1 : 3 : 5-tricarboxylic ester (84); hydrolysis to the free acid (85), boiling with acetic anhydride, followed by dry distillation gave, by progressive loss of carbon dioxide and water, *cyclo*hexanone-4-carboxylic acid (86).

---

[1] W. H. Perkin, jun., *J.C.S.*, 1904, **85**, 416.

The conversion of this compound to terpineol is a fine example of the application of the Grignard reagent. Magnesium methyl iodide was allowed to react with *cyclo*hexanone carboxylic acid ; only the keto- group reacts, the carboxyl group being unattacked by Grignard reagents. The methyl*cyclo*hexanol-4-carboxylic acid so formed (88) is easily converted with hydrobromic acid to the corresponding bromide, which loses hydrogen bromide on heating with alcoholic potash, giving methyl*cyclo*hexene-4-carboxylic acid. The ester of this acid (89) can react with magnesium methyl iodide to give a methyl*cyclo*hexenyl methyl ketone (90) and a still further reaction with magnesium methyl iodide yields the methyl*cyclo*hexenyl dimethyl carbinol, more usually known as inactive α-terpineol (91).



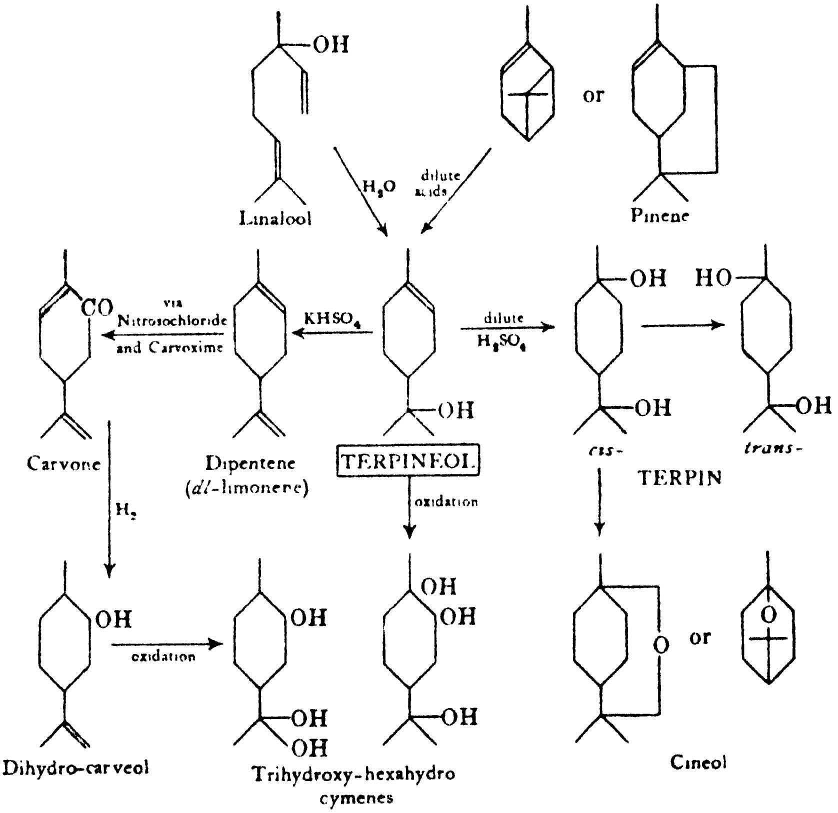
There are several isomeric ‘ terpineols ’, together with the so-called ‘ terpinenols ’, the characteristics of which are summarised in the Table II. The terpineol of commerce is a mixture of the first four compounds of the Table II, and is obtained by dehydrating terpin hydrate with phosphoric acid. It is used as a base for lilac perfumes.

TABLE II

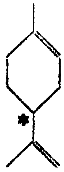
Name	Position of		Physical properties
	—OH group	Double bond	
α-Terpineol	8	1	m. 38–40°, b. 218–219° $[\alpha]_D + 98{\cdot}5°$
β-Terpineol	1	8	m. 32–33°, b. 209–210°
γ-Terpineol	1	4^{8}	m. 69–70°, b. decomp.
Terpinenol-1	1	3	b. 208–210°
Terpinenol-4	4	1	b. 209–212° $[\alpha]_D + 25{\cdot}4°$
Piperitol	3	1	b. 210° decomp.

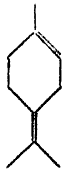
TRANSFORMATIONS OF α-TERPINEOL

The scheme below shows the various directions in which α-terpineol may be transformed by various reagents :—



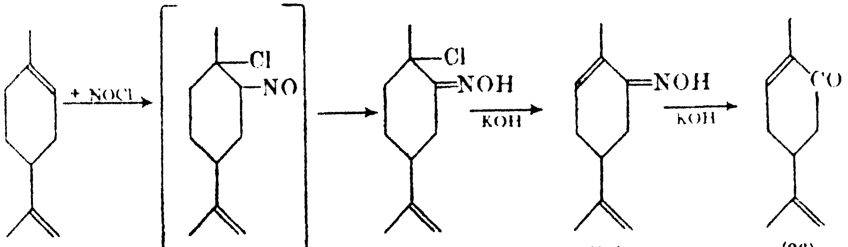
It will be seen that α-terpineol, by its decompositions, is linked with many other terpenes. Thus, when heated with potassium hydrogen sulphate, dipentene is obtained by the loss of the elements of water, a reaction which could have taken place in two ways to give one of the following :—


(92)


(93)

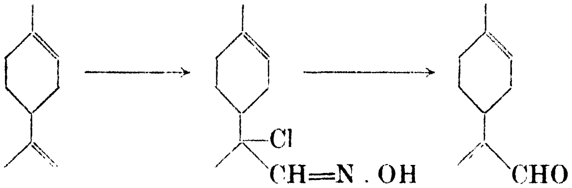
Since dipentene has been shown to be a racemic mixture of D- and L-limonene it must have an asymmetric structure, which can only reside in the carbon atom marked (*) in (92), which formula, therefore, represents the dipentene structure.

Dipentene itself is capable of some interesting transformations ; it forms a nitrosochloride (94) which can be hydrolysed to carvone, the main constituent of oil of carraway seed. The action of alcoholic alkali on the nitrosochloride is dual ; it serves to eliminate hydrogen chloride and to hydrolyse the oxime group (95).



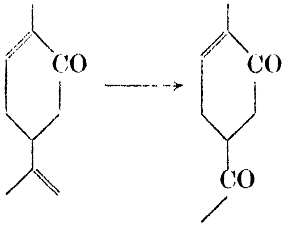
(94) (95) (96)

The addition of the nitrosyl chloride is known to take place to the nuclear double bond, since the substance produced has the properties of a ketoxim, (94) ; had addition taken place to the side-chain double bond (since the chlorine presumably, attaches to the carbon carrying least hydrogen) an aldoxime (97). would have been obtained, yielding an unsaturated aldehyde on hydrolysis (98)e



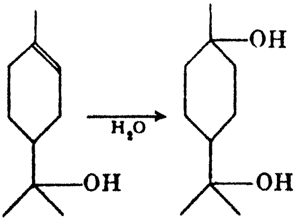
(97) (98)

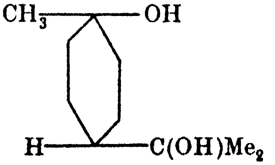
The structure is further confirmed by oxidation of carvone with loss of CO_2 to the diketone (99), which would not take place had the original reaction not taken the course specified.

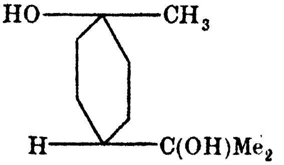


(99)

Reverting to α-terpineol, the double bond is capable of adding on the elements of water, in the presence of dilute sulphuric acid to give 1, 8-terpin (100).



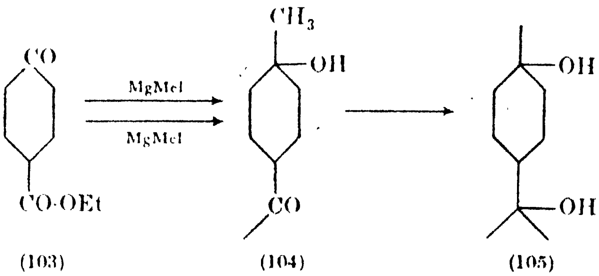


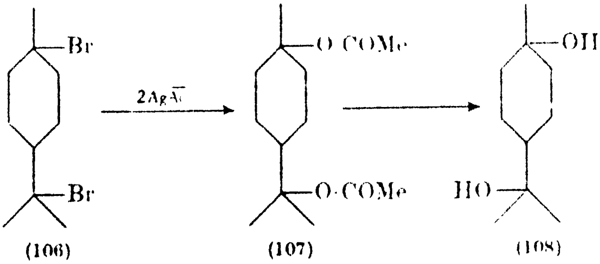


cis- *trans-*

(100) (101) (102)

If it be assumed, for a moment, that the addition takes place as shown in (100), the product can exist in *cis* and *trans* forms (101) and (102) ; from evidence obtained from chemical reactions, it is deduced that the terpin obtained directly from terpineol is the *cis*- form. The structure of the compound is confirmed by its synthesis from *cyclo*hexanone-4-carboxylic ester (103) which, in contradistinction to the corresponding acid, can react with two molecular proportions of magnesium methyl iodide to give the methylhydroxy*cyclo*hexanyl methyl ketone (104), which is converted by a third molecule of magnesium methyl iodide to *cis*-terpin (105), m. 104°. This product is identical with the *cis*-terpin from terpineol. *Trans*-terpin (108), m. 157° is obtained from dipentene dihydrobromide (106) by the action of silver acetate in acetic acid. The di-acetate so produced (107) gives *trans*-terpin on hydrolysis with alkali. *Cis*- and *trans*- terpins differ considerably, the former forming a monohydrate, while the latter does not react with water.





CINEOLE

The essential oils of cajuput, eucalyptus and wormseed contain cineole (eucalyptol) $C_{10}H_{18}O$. This substance behaves as an ether, but also has the property of combining with acids to form salts, such as the phosphate, arsenate and ferrocyanide ; it can also form double compounds with phenol ; the seat of activity is presumed to be the ether oxygen.

Cineole is readily obtained by the action of mild dehydrating agents on *cis*-terpin—no deep-seated change of structure has taken place, since the cineole is readily converted back into *cis*-terpin dibromide by concentrated hydrobromic acid (110). Since the oxygen atom of cineole is of the ether type, there is good reason for assigning to cineole the structure (109).*

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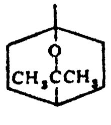
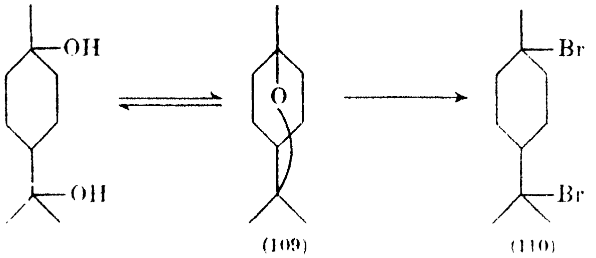
* Cineole is usually written

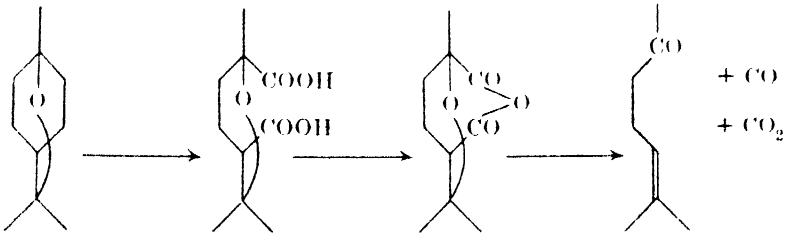


the extended formula (109) is retained here in order to clarify the relation with the terpins.



(109) (110)

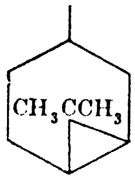
This is further confirmed by degradation of cineole through the following stages :—



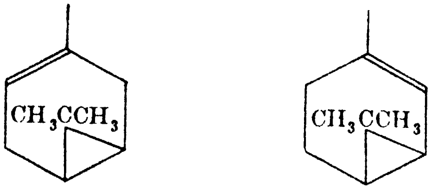
Oxidation of cineole yields cineolic acid, the anhydride of which breaks up on distillation to methyl heptenone and oxides of carbon.

THE CARONE SERIES

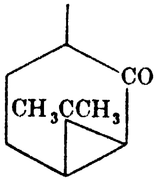
The parent of this series, carane (111), is seldom met with, but Simonsen



(111)

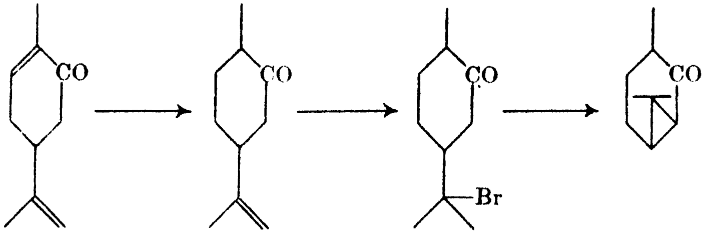


(112)



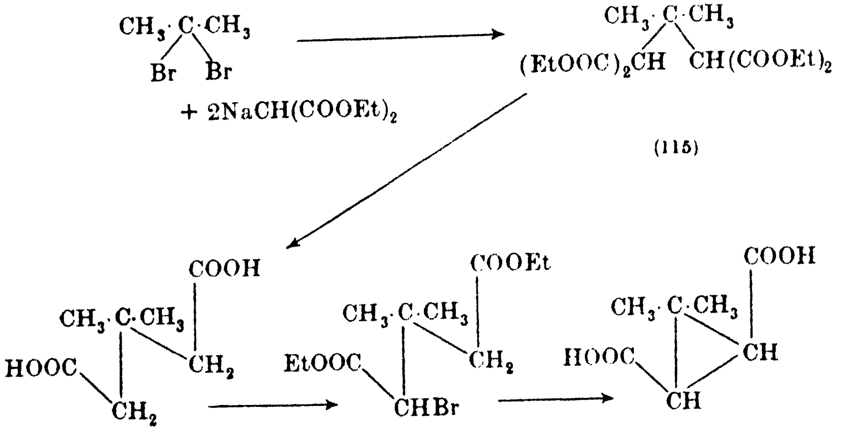
(113)

has separated the carenes (112) from the natural oils of *Pinus longifolia* and a species of *Andropogon*. Carone, the ketone (113) b. 210°, is an important link between the terpineol and dipentene family on the one hand, and the carane and vestrylamine group on the other. Carvone (114) is reduced by zinc dust and alcoholic potash, at its nuclear double bond to dihydrocarvone, which forms a hydrobromic acid addition product (116). The latter, on treatment with alcoholic potash, loses hydrogen bromide, but does not regenerate dihydrocarvone; instead, carone is obtained (117). The existence of the *cyclo*propane ring in carone is revealed by oxidation to caronic acid (118) (*gem*-dimethyl*cyclo*propane-2 : 3-dicarboxylic acid), synthesised in 1899 by Perkin;



(114) (116) (117)

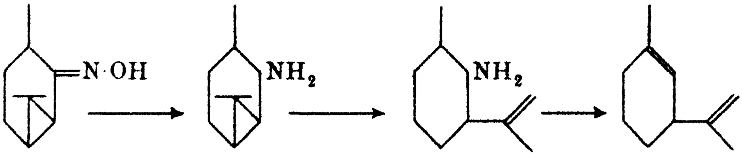
since then, other syntheses have been evolved, e.g. the interaction of excess of sodio-malonic ester with 2 : 2-dibromopropane followed by hydrolysis to ββ′-dimethylglutaric acid. The ester of this acid brominates in the α-position to give α-bromo-ββ′-dimethylglutaric ester, which, on hydrolysis with alcoholic potash, not only loses hydrogen bromide to form the *cyclo*propane ring, but is also hydrolysed, thus producing *cis*- and *trans*-caronic acids (118).



(115)

(118)

The conversion of carone through its oxime (119) to carylamine (120) (sodium and alcohol reduction), and the rearrangement of carylamine into



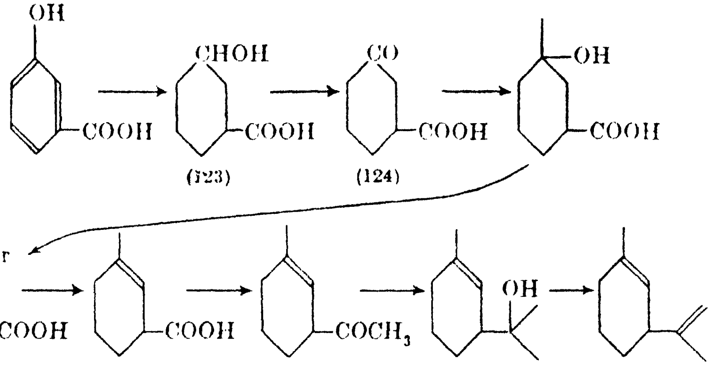
(119) (120) (121) (122)

vestrylamine (121) provides a very important link with the *m*-cymene series, since when vestrylamine hydrochloride is heated it loses ammonium chloride to give carvestrene (122). The authenticity of this transformation series, ending in carvestrene, is confirmed by the synthesis of the latter compound by Perkin and Tattersall in 1907.[1]

---

[1] Perkin and Tattersall, *J.C.S.*, 1907, **91**, 480.

m-Hydroxybenzoic acid is reduced by sodium and alcohol to the hexahydro compound (123); oxidised with chromic acid to *cyclo*hexanone-3-carboxylic acid (124), which then undergoes a series of reactions exactly parallel to those



(123) (124) (125) (126)

for obtaining terpineol, resulting in the *m*-analogue of that substance (125) (3-methyl-2-*cyclo*hexenyl dimethyl carbinol). The properties of this substance resemble greatly those of terpineol itself and, with acid potassium sulphate, dehydration takes place to carvestrene (126).

Carvestrene is the racemic form of the D-sylvestrene originally isolated from pine oil by Atterberg in 1877. Sylvestrene, b. 175°, $[\alpha]_D$ + 67·5° in chloroform, is also obtained from carene, when the latter is treated with hydrogen chloride.

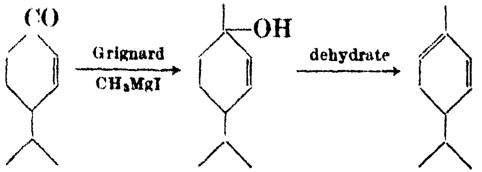
The Phellandrenes

The phellandrenes are two members of a large family of menthadienes (or 1-methyl-4-*iso*propyl*cyclo*hexadienes); the positions of the bonds are shown in Table III.

TABLE III

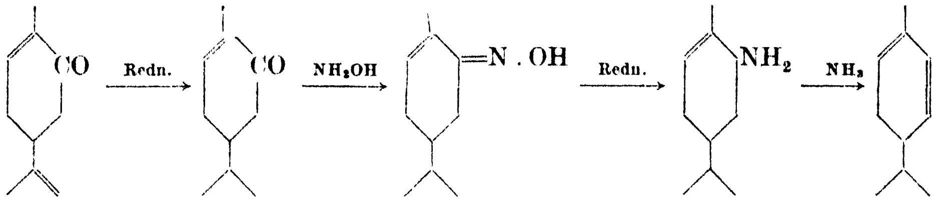
Name	Positions of double-bonds	
α-Terpinene .	1	3
β-Terpinene .	1(7)	3
γ-Terpinene .	1	4
α-Phellandrene .	1	5
β-Phelladrene .	1(7)	2
Limonene .	1	8(9)
Terpinolene .	1	4(8)
ψ-Limonene .	1(7)	8(9)

α-Phellandrene (128), found naturally in the oils of elemi, eucalyptus and bitter fennel, is the 1, 5 diene, and has been synthesised (*a*) from *iso*propyl*cyclo*hexene-2-one-4 (127) through the following simple steps :—

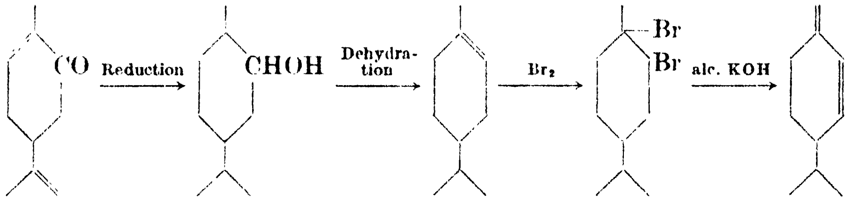


(127) (128)

(*b*) from carvone.

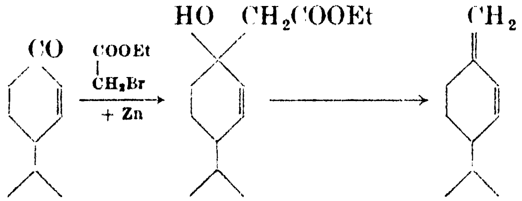


β-Phellandrene is the 1(7), 2 diene (129), and has been synthesised from carvone, thus :—



(129)

and also from *iso*propyl*cyclo*hexene-2-one-4 (130) by condensation with ethylbromoacetate and zinc, to give the ester (131), which, on conversion to the acid

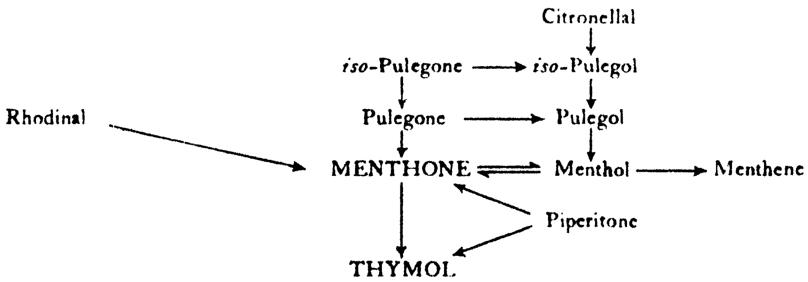


(130) (131) (132)

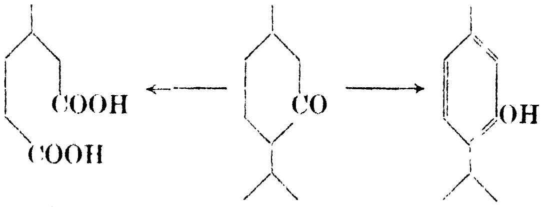
and heating, yields β-phellandrene (132).

The Menthone Family

The schematic relations between the members of this group are shown below :—

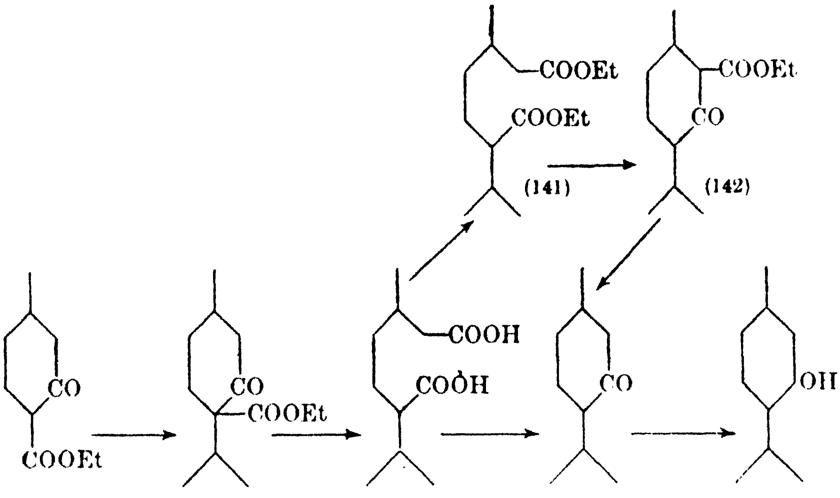


Menthol, the *l*-form of which is the main odoriferous principle of peppermint, is widely used in medicine for its antiseptic and analgesic properties. The Dutch botanist, Gambius, recognised it as a crystalline compound in 1771 and called it "*camphora europæa menthæ piperitidis.*" Its formula $C_{10}H_{20}O$, and the fact that it is easily converted to the ketone menthone $C_{10}H_{18}O$ by oxidation, show it to be a secondary alcohol. The key to the structure of menthol lies in the degradation products and synthesis of menthone. Oxidation of menthone yields a hydroxymenthylic acid and by stronger action β-methyl adipic acid (133) from which it may be deduced that the two —COOH groups of β-methyl adipic acid represent the point of attachment of the *iso*propyl group and the



(133) (134) (135)

position of the carbonyl group. Since menthone can be converted to thymo (135) by bromination, and reduction, the *iso*propyl group must be *para*- to the methyl and the formula of menthone that shown in (134), suggested by Semmler in 1892. Confirmation of this structure was obtained by the synthesis of Kötz and Schwarz in 1907.[1] By reacting 3-methyl*cyclo*hexanone-6-carboxylic ester (136) with sodium ethoxide and *iso*-propyl iodide, a menthone carboxylic ester (137) was obtained. This can be converted to menthone itself by boiling with concentrated alkali when the ring is opened, hydrolysis and loss of carbon



(141) (142)

(136) (137) (138) (139) (140)

dioxide ensue, and a methyl *iso*-propyl pimelic acid is formed (138). Distillation of the calcium salt of this acid yields menthone (139) ; reduction of menthone yields menthol (140). The ester of δ-methyl-α-*iso*propylpimelic acid (141) will, on treatment with sodium, undergo an internal keto-ester reaction (cf. aceto-acetic ester from ethyl acetate), giving the menthone carboxylic ester (142). The corresponding acid gives menthone and carbon dioxide on heating.

The stereochemistry of the menthol group is complicated by the fact that menthol has three, and menthone two, asymmetric carbon atoms, whilst in addition *cis*- and *trans*- forms are known. Considerable work has been carried out by Read and Grubb on the menthol structures by examining the reaction velocities of menthols and *iso*menthols. Their configurations are shown in the following table :—

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[1] Kötz and Schwarz, *Ann.*, 1907, **357**, 209.

TABLE IV

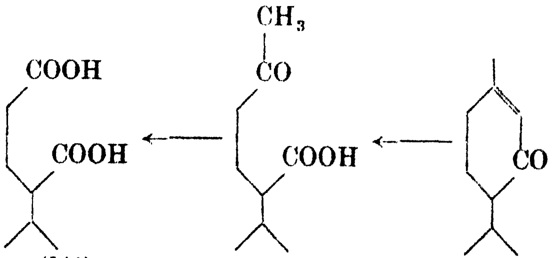
	Menthols	Neomenthols	*iso*-menthols	Neo-*iso*-menthols
Structure . .	CH_3—|—H HO—|—H H—|—*i*-Pr	CH_3—|—H H—|—OH H—|—*i*-Pr	CH_3—|—H H—|—HO *i*-Pr—|—H	CH_3—|—H HO—|—H *i*-Pr—|—H
M.P. of DL- . .	35–38°	53	53·5°	14°
M.P. of D- or L- .	42–43°	— 22°	82·5°	− 8°
$[\alpha]_D$ . . .	— 49·6°	+ 20·7°	+ 25·9°	+ 2·2°*
$[\alpha]_D$ of corresponding menthylamine .	— 44·5°	+ 15·1°	+ 29·0°	+ 2·3°

* Figure obtained from alcoholic solution.

PIPERITONE

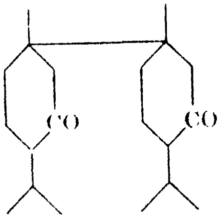
Piperitone has a special economic interest in that it is commercially available in very large quantities from certain species of the genus *Eucalyptus*. *Eucalyptus* comprises three-quarters of the vegetation of Australia and from *E. dives* piperitone may be extracted readily since this species yields 4 per cent. of oil containing 40–50 per cent. of piperitone. Since this species of Eucalyptus is a rapid grower, even from felled stumps, piperitone might easily be obtained in sufficient quantity to serve as a raw material for manufacturing processes.

Piperitone has the empirical formula $C_{10}H_{16}O$, and may be hydrogenated at 35° in the presence of colloidal palladium to a mixture of menthones. The structure of piperitone must therefore be that of menthone, except for the presence of a double bond in the former. Oxidation of piperitone yields a series of compounds, the simplest of which is α-*iso*propylglutaric acid (144).



(144) (145) (146)

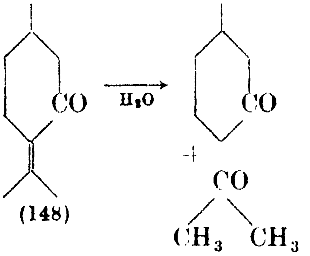
The existence of the intermediate product 2-methylheptanone-6-carboxylic acid-3 (145) proves that the formula of piperitone must be (146). This methylheptanone carboxylic acid can be synthesised by the action of the Grignard reagent on the half ester of α-*iso*propylglutaric acid. One of the most characteristic reactions of piperitone is the formation of 1 : 1′-bis-menthone (147) on reduction with sodium amalgam and aqueous alcohol.



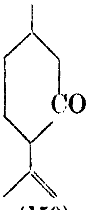
(147)

PULEGONE

Pulegone, from oil of pennyroyal, is isomeric with piperitone, and, like it, may be reduced catalytically to menthone, from which it follows that pulegone and piperitone differ only in the position of the double bond. Pulegone (148) and water, when heated at 250° C., yield acetone and methyl *cyclo*hexanone-3 (149), from which it is clear that the double bond is in the semi-cyclic position shown in (148). Pulegone may be converted to *iso*-pulegone by heating the hydrobromide of the former with basic lead nitrate ; the reverse process takes place when *iso*-pulegone is heated with baryta. This shows that pulegone and *iso*-pulegone differ only in the position of the double bond, and the relation of citronellal and *iso*-pulegone indicate that this is situated in the side-chain, as in (150).



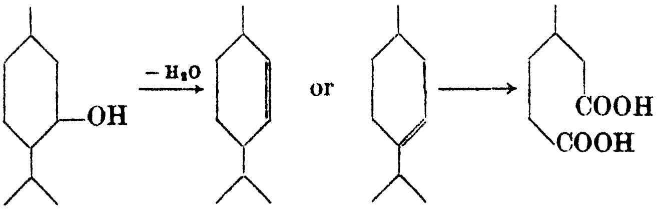
(148) (149)



(150)

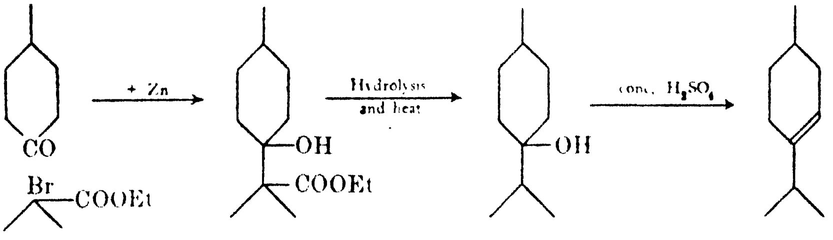
MENTHENE

The menthene obtained by the dehydration of menthol must, since it contains one double bond have one of the two formulæ (151) and (152) ; its oxidation to β-methyl adipic acid (153) shows that the second of these formulæ is the correct one, and this has been confirmed by Wallach's synthesis of this menthene. He condensed 4-methyl*cyclo*hexanone (154) with α-bromo*iso*butyric ester in the presence of zinc, giving an ester (155), the corresponding acid from which

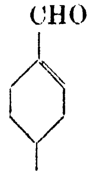


(151) (152) (153)

lost carbon dioxide on heating forming menthanol (156); this, on warming with sulphuric acid, yielded menthene (157) identical with that from menthol.



(154) (155) (156) (157)

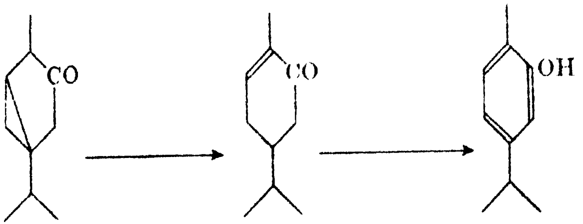


(157*a*)

l-Perilla aldehyde (4-*iso*propenyl-2, 3, 4, 5-tetrahydrobenzaldehyde) (157*a*) is an unusual type of aldehyde derived from *Perilla nankinensis*; it has a pleasant smell and its *anti*aldoxime is 2000 times as sweet as sugar (i.e., four times as sweet as saccharin). It has not been synthesised.

THE DICYCLIC TERPENES

Of the dicyclic terpenes having a *cyclo*propane ring, the caranes have already been mentioned. The thujone series provides a link with the monocyclic terpenes, since thujone itself is isomeric with pulegone and piperitone, but does not show the properties of an unsaturated compound. This points to the existence in thujone of a secondary ring, which has been formulated as in

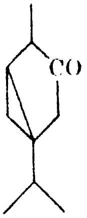


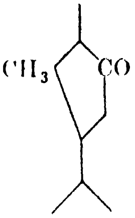
(158) (159) (160)

(158). Thujone occurs in sage and wormwood oils; heat converts it to carvotanacetone (159) which by bromination and reduction gives carvacrol (160), thus establishing the main points of the structures. Thujone itself yields carvacrol when boiled with ferric chloride.

The existence of the bridge link in thujone is confirmed by its conversion to *iso*thujone, a *cyclo*pentanone derivative (161) on warming with 40 per cent. sulphuric acid. The identity of *iso*thujone was established by Semmler through a series of oxidative degradations. Sabinene (162), $C_{10}H_{16}$, one of the main constituents of marjoram oil, has a bridge similar to that of thujone.

Its most characteristic reaction is the loss of a $—CH_2$ group on oxidation, forming sabinaketone $C_9H_{14}O$ (163). The existence of the unusual bridge-link





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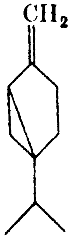
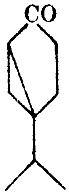
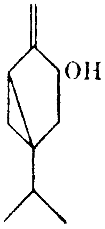


(162)

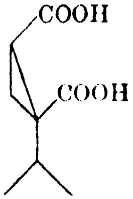


(163)

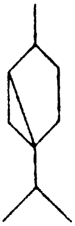
in this group of compounds is demonstrated by the oxidation of sabinol (hydroxysabinene) (164) to α-tanacetone dicarboxylic acid (165). Thujane itself, b. 157° (165*a*), can be obtained by the catalytic reduction of sabinene (162).



(164)



(165)



(165a)

References made above to 'thujone' are intended to refer to α-thujone, b. 201°, $[\alpha]_D$ − 10°, found in oils of thuja and absinthe. The stereoisomeride, β-thujone, is less frequently met with, but has been isolated from tansy and wormwood.

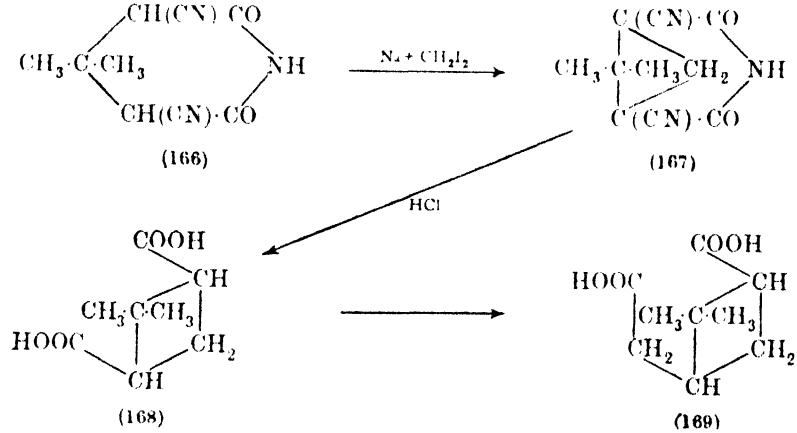
THE PINENE GROUP

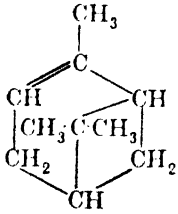
Pinene, $C_{10}H_{16}$, is an optically active substance; its *d*-form (australene) occurs in Scandinavian and German turpentines, and the *l*-form (terebenthene) in French turpentine. Much information concerning the structure of pinene may be obtained from its progressive oxidation, the compounds formed being listed in Table V below.

TABLE V

	Substance	Formula	Properties
I	Pinonic acid (oxidation of pinene with potassium permanganate)	$C_7H_{12}\left\{\begin{matrix}COOH\\COCH_3\end{matrix}\right.$	A monobasic acid methyl ketone No double bonds
II	Pinic acid From pinonic acid with bromine + alkali	$C_7H_{12}(COOH)_2$	A dibasic acid
III	Norpinic acid	$C_6H_{10}(COOH)_2$	A dibasic acid having one $—CH_2$ less than pinic acid. Has been synthesised

Originally the structure of pinene was deduced from other considerations, but the synthesis of norpinic acid by Kerr in 1929 gives a simpler means by which the formula of pinene may be deduced. Dimethyldicyanoglutarimide (166) in the form of its sodio-derivative reacts readily with methylene iodide to give the methylene compound (167) which is hydrolysed to norpinic acid (168). Since norpinic acid is obtained by loss of —CH_2 from the analogous dibasic acid, pinic acid, the structure of the latter must be (169). It may also be argued that pinonic acid is the corresponding methyl ketone (170). The alternative formula (171) is ruled out on the ground that pinene yields *p*-cymene

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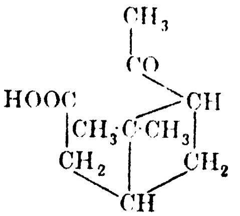
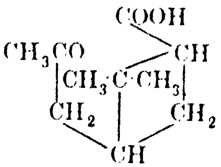
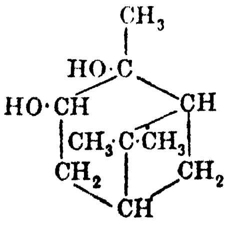

(170)

or


(171)

when heated with iodine; the alternative formula would yield *m*-cymene. Since pinonic acid is formed from pinene it is to be supposed that the $>$CO and —COOH groups of the former indicate the position of the double bond in the latter; hence pinene is assumed to have the structure (172).

The formula of pinene is in keeping with its reactions, more particularly those shown in the scheme below :—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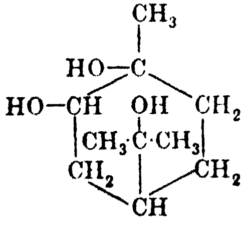
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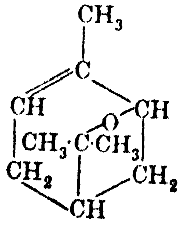
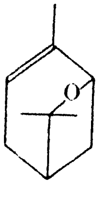

(175)

Step I.—Pinene is oxidised by dilute potassium permanganate to pinene glycol (Sobrerol) (173) $C_{10}H_{16}(OH)_2$.

STEP II.—Pinene glycol, when warmed with very dilute hydrochloric acid passes, presumably through intermediate (174), into pinol (175) $C_{10}H_{16}O$.

STEP III.—Pinol, oxidised with potassium permanganate yields terpenylic acid (176), the formula of which has previously been established (p. 689).



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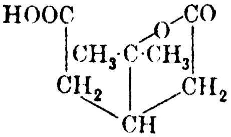
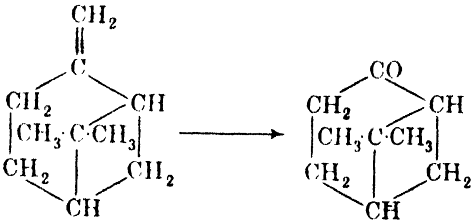


(176)

Nopinene (β-pinene) (177) is isomeric with pinene and constitutes two-fifths of French turpentine; it can be converted readily to nopinone (178) in exactly the same way as sabinene to sabinaketone. This points to the existence of the semi-cyclic double bond, whilst the remainder of its structure follows from its oxidation to norpinic acid.



(177) (178)

CAMPHORS

Some confusion arises from the fact that the term "camphor" was applied originally to any solid terpene-like substance, and in addition to the true terpenes the group originally contained hydrocarbons ("stearoptenes") and sesquiterpene alcohols. The following is a summary of the camphors most frequently met with :—

I.—*Ordinary, Japanese or Laurel Camphor.*—From the camphor laurel, *Cinnamomum camphora*, and in smaller quantity from essential oils of lavender, rue, rosemary and sage, etc. Hexagonal prisms, m.p. 178°, b.p. 204° C. $[\alpha]_D$ + 44·2° in 20 per cent. solution in alcohol.

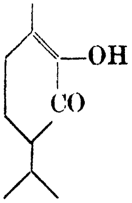
II.—*Lævo or Matricaria Camphor.*—This is the antimer of ordinary or *dextro*-camphor. It is obtained by oxidising *l*-borneol, or from the oil of *Matricaria parthenium*.

III.—*Synthetic camphor* is, of course, optically inactive.

IV.—*Borneo, Malayan or Drybanalops camphor* is *d*-borneol, m.p. 204° b.p. 212°. It is obtained from the wood of *Drybanalops aromatica*.

V.—*Ngai camphor* is the lævo isomer of the previous substance found in *Blumea balsamifera*.

VI.—*Buchu camphor* or diosphenyl, from *Barosma* leaves is not a true camphor, and is of the structure shown in (179). Its inclusion in the series of camphors is purely due to its solid and aromatic nature; for similar reasons the early chemists included in the family "mint camphor"—menthol.



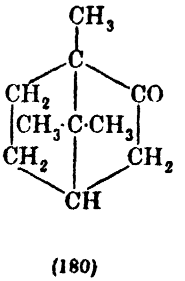
(179)

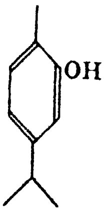
ORDINARY CAMPHOR

The industrial value of camphor is very high; apart from its use in medicine as counter-irritant and local anæsthetic, it is used in large quantities for the manufacture of celluloid and of smokeless propellants. So far, no entirely satisfactory substitute for its use in the celluloid industry has been found.

Camphor, $C_{10}H_{16}O$, is obtained by distilling with steam the wood of the camphor tree (*Laurus camphora* or *Cinnamomum camphora*). The camphor entering commerce differs in rotatory power according to the district in which it has been grown, but is mostly dextro-rotatory.

The first point to be established in a consideration of its structure is the fact that it is a ketone, whilst from the ease with which it is converted to its *iso*-nitroso compound, it is probable that a methylene group is in a position adjacent to the carbonyl group ($—CH_2 . CO$). *p*-Cymene is obtained when camphor is heated with dehydrating agents, thus establishing the *a priori* case for a terpene structure. Since, however, camphor has two hydrogen atoms less than the formula $C_{10}H_{18}O$ of a simple monocyclic terpanone, and since it shows no properties consistent with the presence of a double bond, the presence of a second ring is probable. The position of the keto-group is defined by the oxidation of camphor to carvacrol (181) by iodine, and the formula for camphor shown below was suggested by Bredt in 1893 (180).



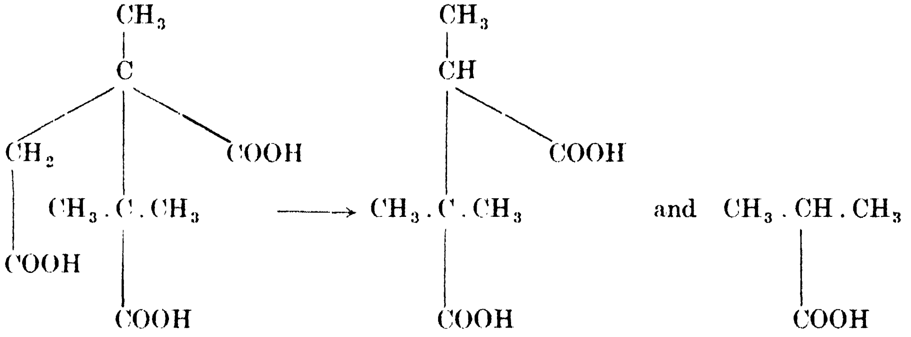


(180) (181)

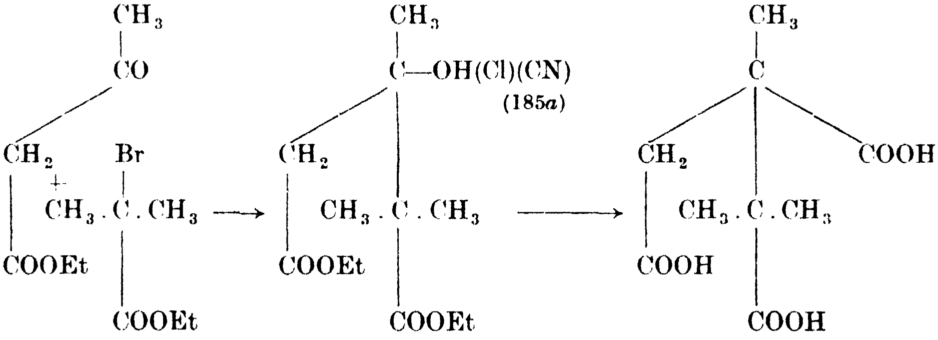
In this formula the only real issue is the position of the secondary ring system, which has been settled by a consideration of the oxidation products of camphor.

When camphor is oxidised it yields, progressively, camphoric acid $C_{10}H_{16}O_4$, and camphoronic acid $C_9H_{14}O_6$.

In suggesting the formula (182) for camphoronic acid Bredt was guided by its thermal decomposition to trimethyl succinic (183), *iso*-butyric (184) and carbonic acids. Confirmation of this structure was obtained by Perkin and Thorpe in 1897 by synthesis. The Reformatski reaction between acetoacetic ester, α-bromo *iso*butyric ester and zinc furnishes β-hydroxytrimethylglutaric ester (185). By usual methods, the hydroxyl group of this compound may be replaced by chlorine and by the —CN group (185*a*); hydrolysis then yields optically inactive camphoronic acid (186).

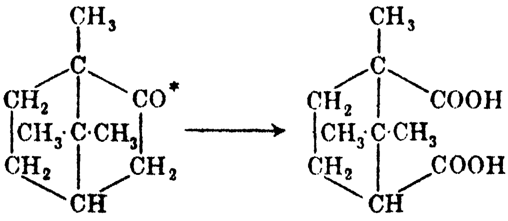


(182) (183) (184)



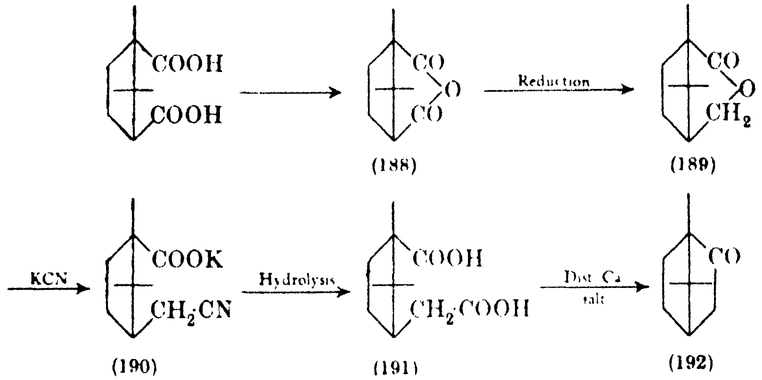
(185) (186)

Camphoric acid (187), since it is a dibasic acid, and not ketonic, must have been obtained from camphor by attack at the carbonyl group (*); the well-known vulnerability of a methylene group adjacent to the carbonyl group



(187)

makes it probable that such a group furnishes the second carboxyl of camphoric acid, indicating (187) as the tentative formula for the latter compound. This is further confirmed by the tendency of camphoric acid to give an anhydride and by the reconversion of camphoric acid to camphor according to the following scheme :—

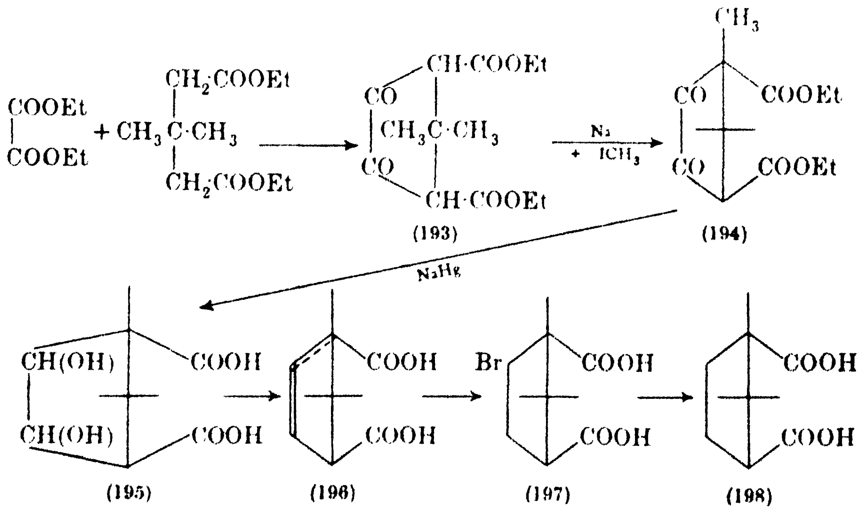


(188) (189)

(190) (191) (192)

Camphoric anhydride (188) is reducible by sodium amalgam, at the $>$CO group (*) to campholide (189). Campholide reacts with potassium cyanide to give the potassium salt of homocamphoric nitrile (190), the corresponding acid (191) being obtained by hydrolysis. Distillation of either the lead or calcium salt of homocamphoric acid yields camphor (192).

Finally, several independent syntheses of camphoric acid have confirmed the structures already put forward. The synthesis of Komppa in 1903 commenced with an ester condensation between oxalic ester and $\beta\beta$-dimethylglutaric ester, producing diketoapocamphoric ester (193), which, with sodium and methyl iodide gave diketocamphoric ester (194).

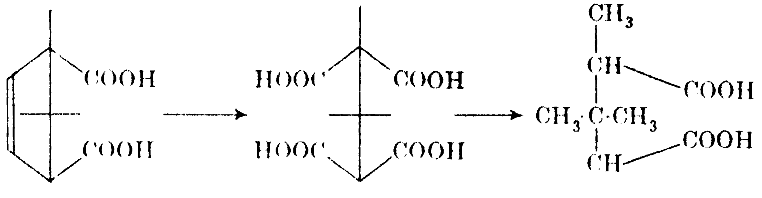


(193) (194)

(195) (196) (197) (198)

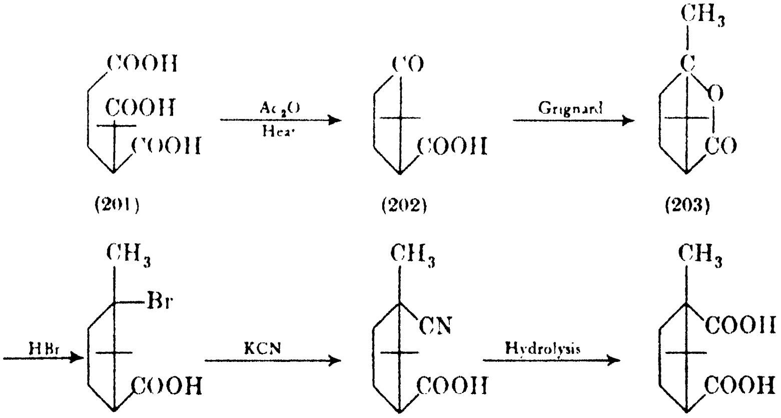
Reduction with sodium amalgam in an inert atmosphere gives the corresponding alcohol (195), the ester groups being hydrolysed at the same time.

Further reduction with red phosphorus and iodine gives the unsaturated derivative (196), the hydrobromide of which (197) is reduced by zinc dust and acetic acid to camphoric acid (198). The position of the double bond in acid (196) and of the bromine in (197) has been settled by the oxidation of (196) with formation of trimethylglutaric acid (200), clearly obtained through the intermediate substance (199) :—



(199) (200)

Perkin's synthesis of camphoric acid is shown in the following scheme. 1, 1-Dimethylbutane-1, 2, 4-tricarboxylic acid (201) on heating with acetic anhydride cyclises with loss of carbon dioxide and water to give 2, 2-dimethyl-*cyclo*pentanone-3-carboxylic acid (202). This yields, with magnesium methyl



(201) (202) (203)

(204) (205) (206)

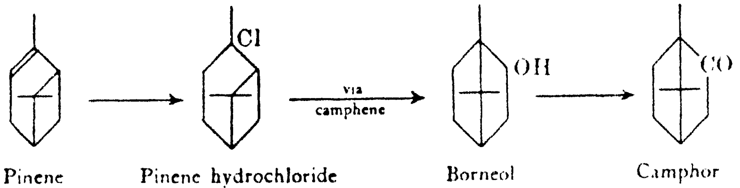
iodide, a hydroxy- acid, which passes to the lactone (203). Conversion through the bromo- and cyano- compounds (204) and (205) to camphoric acid (206) proceeds by orthodox steps.

Clearly, the combination of the synthesis of camphoric acid with its conversion to camphor constitutes a complete synthesis of the latter body.

SYNTHETIC CAMPHOR

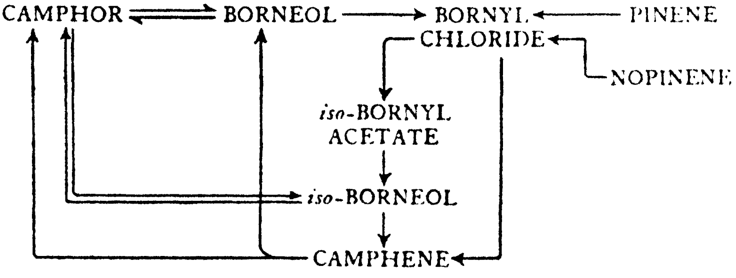
The synthesis of camphor just described obviously has no commercial value, and camphor is synthesised industrially from freshly fractionated pinene. When freshly distilled pinene is cooled and dry hydrogen chloride is passed in, pinene hydrochloride (bornyl chloride) is obtained in white crystals. These are filtered by pressure from any liquid material and fractionated, pinene hydrochloride boiling without decomposition at 207–208° C. This process gives a good yield of the hydrochloride, which is converted to camphene by heating with slaked lime to 130–160° ; an improvement in this phase of the process, suggested by Reychler, is the use of phenol with half an equivalent of sodium hydroxide, which, when heated with pinene hydrochloride in an autoclave for ten hours at 150–170° gives a good yield of camphene.

The camphene, purified by fractionation, is treated with acetic and sulphuric acids when borneol and *iso*-borneol are obtained. These are readily oxidised to camphor, in presence of a catalyst, preferably by aerial oxidation. These reactions are shown below :—



Many attempts have been made to convert pinene directly into borneol, and some measure of success has attended the use of oxalic acid for this purpose. Pinene and anhydrous oxalic yield 30 per cent. of borneol when heated together in vacuo at 125°.

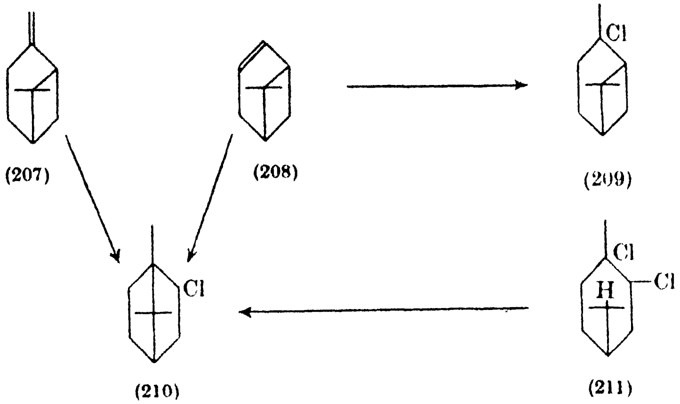
Borneol, the alcohol corresponding to camphor, is a naturally occurring substance (from *Drybanalops aromatica*), and may be obtained together with *iso*-borneol by reducing camphor with sodium and alcohol. It yields a chloride on treatment with hydrogen chloride which occupies a position of importance in the following scheme :—

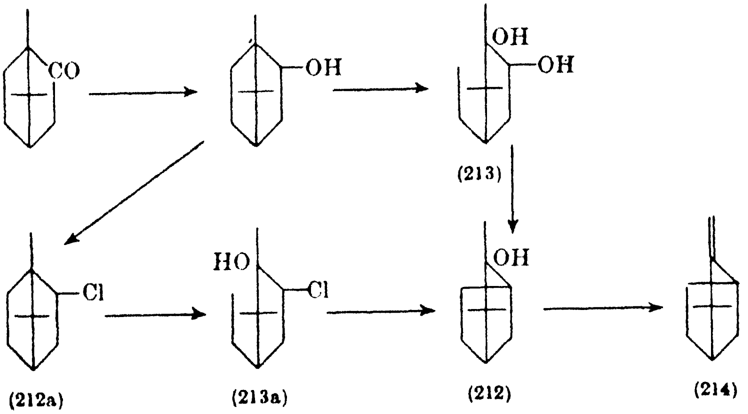


Both nopinene and pinene (207) and (208) yield bornyl chloride (210) on treatment with hydrogen chloride, change in the secondary ring structure being thus obtained, which may take place through the intermediates (209) and (211). A further example of the lability of this type of linkage is the formation of *iso*-borneol (212) from camphor by reduction, which probably takes place through the intermediate stage (213).

The formulæ at top of page 711 again draw attention to the problem of camphene (214). This hydrocarbon $C_{10}H_{16}$ is produced both from borneol by dehydration and from pinene by heating with sodium stearate. It is outside the scope of this work to enter into all the considerations which have led to the general adoption of the Wagner formula for camphene, but the excellent account of the later stages of the problem given by Kon (*J.C.S. Ann. Rep.*, 1932, p. 147) is recommended to those desiring more detailed knowledge.

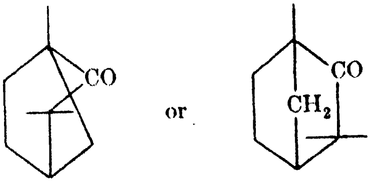
The alternative route for *iso*-borneol is shown in (212*a*) and (213*a*). It is also to be noted that when *iso*-borneol is converted to its chloride and the latter heated with alcoholic potash, camphene (214) is produced.





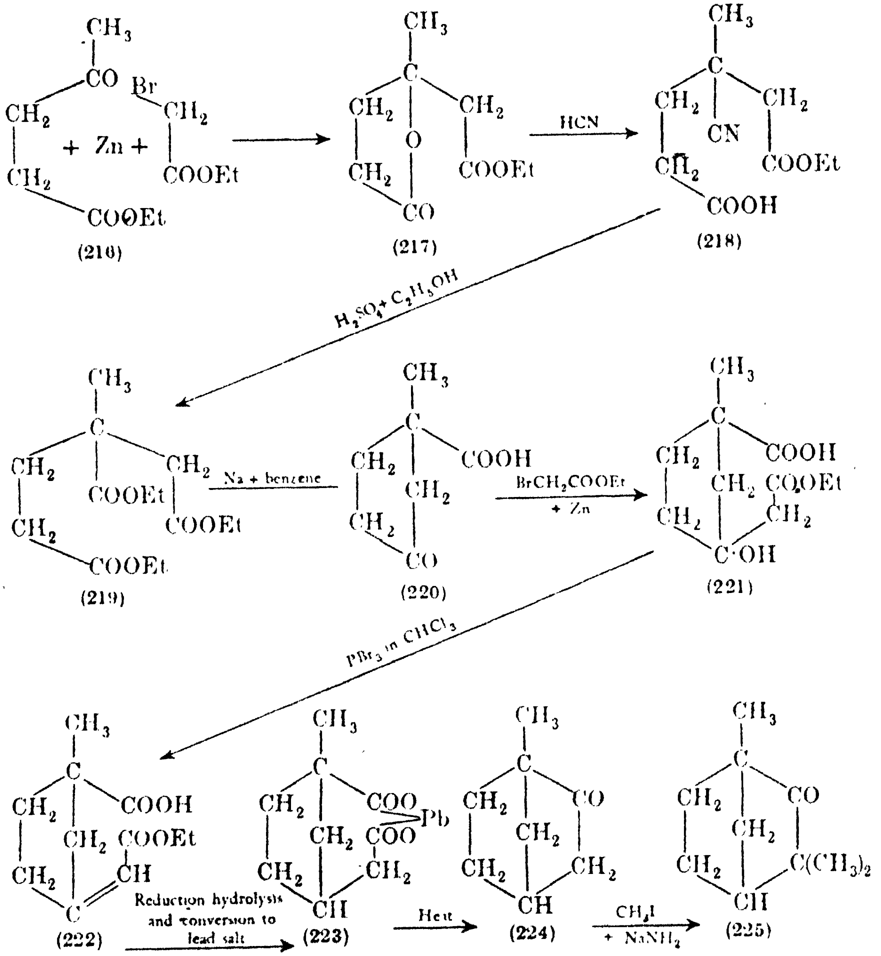
FENCHONE

A new type of ring system is shown by fenchone (215), which occurs in fennel oil and was synthesised by Ruzicka in 1917. Ethyl levulinate (216)



(215)

and bromoacetic ester are condensed in the presence of zinc to form the lactone (217). This adds on the elements of HCN, and the nitrile-acid (218) so formed yields the tri-ester (219) on treatment with alcohol and sulphuric acid. Sodium in benzene suspension brings about an internal acetoacetic ester condensation in the tri-ester furnishing 3-methyl*cyclo*pentanone-1-carboxylic acid-3 (220). Another Reformatski reaction with zinc and bromoacetic ester gives the alcohol (221) which readily loses water on treatment with phosphorus tribromide in chloroform to give the unsaturated ester (222). This, after reduction to the saturated compound, and conversion to the lead salt of the corresponding acid (223), yields on distillation methyl-*nor*-camphor (224). The final conversion to fenchone (225) is achieved by methylating methyl-*nor*-camphor with sodamide and methyl iodide.



The Azulenes

Records going back five centuries show that the essential oils extracted from certain plants—e.g., camomile, possess a blue colour which has in recent years been shown to be due to the presence of deep blue or violet hydrocarbons —azulenes, the parent of which is a C_{15} hydrocarbon. Work carried out by Sherndal[1] showed that if an ethereal solution of the oils be treated with a concentrated phosphoric acid solution, the azulene is extracted, and on dilution of the aqueous phase is regenerated and may be extracted.

---

[1] Sherndal, *J.A.C.S.*, 1915, 37, 167 and 1537.

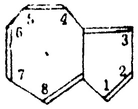
The main azulene compounds of natural occurrence are shown in Table VI below :—

TABLE VI

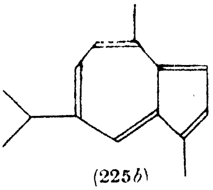
Name	M.P.	Colour	Source
s-Guaiazulene .	m. 30°	Blue needles	From geranium oil, coal-tar, and by the action of sulphur on guaiacum wood, patchouli, and gurjun balsam oils
Vetivazulene .	m. 32°	Violet needles	From vetiver oil, by the action of sulphur
Camazulene .	m. 132°	Blue needles	From camomile oil
Lactarazulene .	—	Blue liquid	Of fungoid origin from *Lactarius deliciosus* (' Blue stales ')

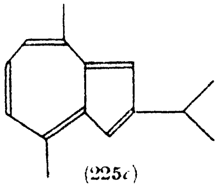
The azulenes form compounds with trinitrobenzene, which can be crystallised, but from which the aromatic nitro body is removed by chromatographic adsorption.

When the pure azulenes are reduced catalytically they take up eight atoms of hydrogen to give hydrocarbons of the formula $C_{15}H_{26}$, but one double-bond still remains unreduced. Refractive index determinations and the fact that azulenes can be converted into naphthalene derivatives led to the suggestion that these substances are *cyclo*pentenocycloheptene derivatives, related to azulene (225*a*).

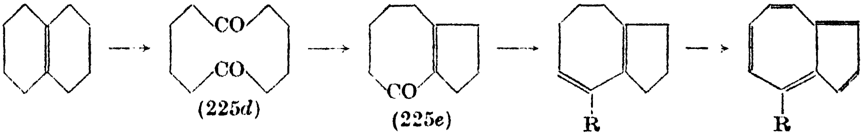


(225*a*)


(225*b*)


(225*c*)

The synthesis of the parent compound has been carried out by Pfau and Plattner,[1] together with that of its homologues substituted in the ' 4 ' position.



(225*d*) (225*e*) (225*f*) (225*g*)

The method is to obtain *cyclo*decandione-1, 6 (225*d*) by the action of ozone on octalin. This is converted to *cyclo*pentenocycloheptanone by dilute sodium carbonate (225*e*), when, by acting on the carbonyl group with a Grignard reagent and dehydrating the alcohol produced, a tetrahydroalkylazulene (225*f*) is obtained ; catalytic dehydrogenation then gives the azulene (225*g*), which is deep blue and indistinguishable spectroscopically from the natural azulene derivatives. In view of their transformation to the corresponding dimethyl-*iso*propylnaphthalenes, *s*-guaiazulene and vetivazulene are regarded as 1, 4-dimethyl-7-*iso*propylazulene (225*b*) and 4, 8-dimethyl-2-*iso*propylazulene (225*c*) respectively. As to the mode of formation of these compounds in nature one has only to rewrite the formula of farnesol to obtain at least one method by which an azulene ring could be obtained :—

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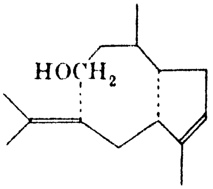
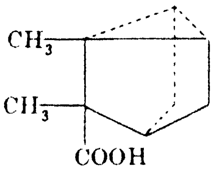
[1] Pfau and Plattner, *Helv. Chim. Acta*, 1936, **19**, 858.



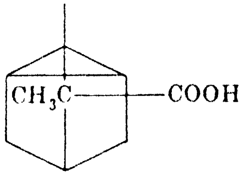
Farnesol

THE SESQUITERPENES

Terpenes containing fifteen carbon atoms—the sesquiterpenes—are plentiful in natural materials, especially in flowers and wood-oils. Their structures are, naturally, more complex than those of the true terpenes, and, in addition, their study is complicated by the fact that they form cage compounds, e.g. those derived from teresantalic acid (226), more usually written (227).



(226)



(227)

It is proposed to discuss only representative sesquiterpenes of prominent interest.

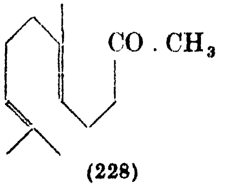
FARNESOL

Farnesol, $C_{15}H_{26}O$, occurs to a very limited extent in oil of cassie (*Acacia farnesiana*), and is best obtained from ambrette seed oil. Its refractivity, ability to add on six hydrogen or bromine atoms and to form a triozonide point to the presence, in its molecule, of three double bonds, and since it oxidises to an aldehyde of the same number of carbon atoms, it is probably a cyclic primary alcohol.

Its structure has been determined by the following steps. Farnesal oxime can be dehydrated to a nitrile, which on hydrolysis yields farnesic acid ; this breaks down on mild oxidation to

$$\begin{array}{l} R\,.\,CH{=}N\,.\,OH \\ \quad\downarrow Ac_2O \\ R\,.\,CN \\ \quad\downarrow \text{Hydrolysis} \\ R\,.\,COOH \end{array}$$

dihydro ψ ionone $CH_3\,.\,COOH$



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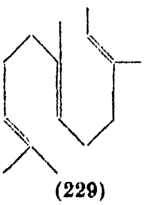

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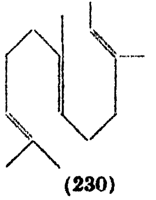
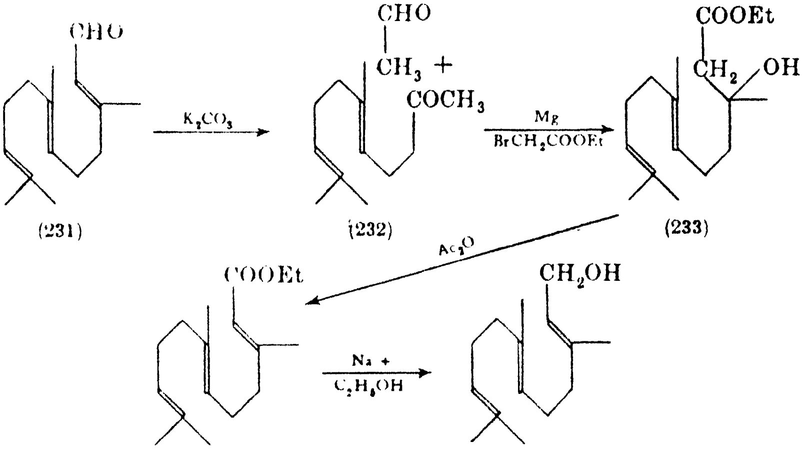


(230)

dihydro-ψ-ionone (228) and acetic acid ; thus indicating the formula (229) for farnesic acid and (230) for farnesol. This has been confirmed by Verley, who

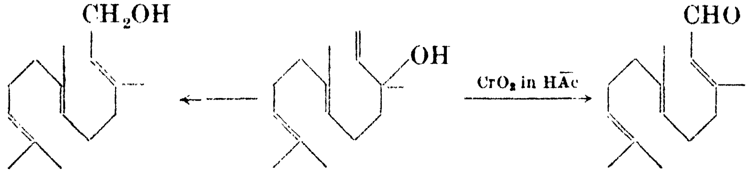


(231) (232) (233)

(234) (235)

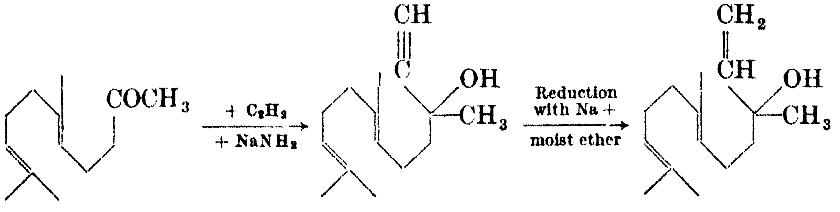
showed that farnesal on heating (231) with potassium carbonate, is broken down into acetaldehyde and dihydro-ψ-ionone (232) just as citral is broken down under similar conditions to methylheptenone and acetaldehyde. Synthesis of farnesol was carried out by allowing dihydro-ψ-ionone, bromacetic ester and magnesium to react together ; a hydroxy ester (233) was obtained which readily lost water on boiling with acetic anhydride to give farnesic ester (234) ; reduction of this with sodium and alcohol yields some farnesol (235), mixed with a larger quantity of dihydrofarnesol.

Nerolidol (237) (formerly " peruviol "), found in various blossoms (" Syringa " = *Philadelphus coronarius*) is isomeric with farnesol (236) and converted into it by boiling with acetic anhydride. It appears that this change is parallel to that of linalool into nerol ; further, nerolidol, when oxidised by an acetic acid



(236) (237) (238)

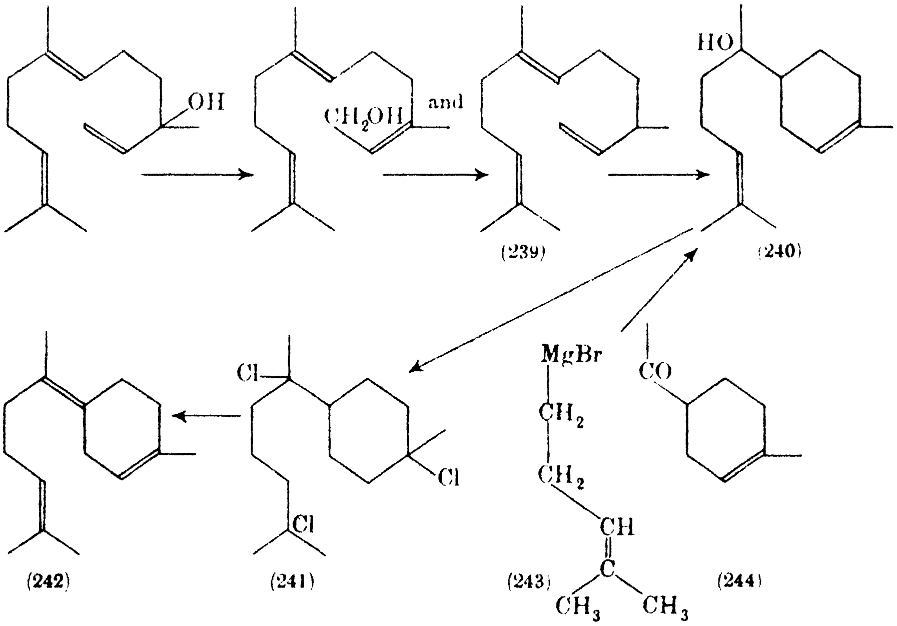
solution of chromic acid yields farnesal (238) ; this, again, is parallel to the conversion of linalool by the same reagent to citral, and points to the formula (237) for nerolidol. Confirmation comes through Ruzicka's synthesis from dihydro-ψ-ionone, thus :—



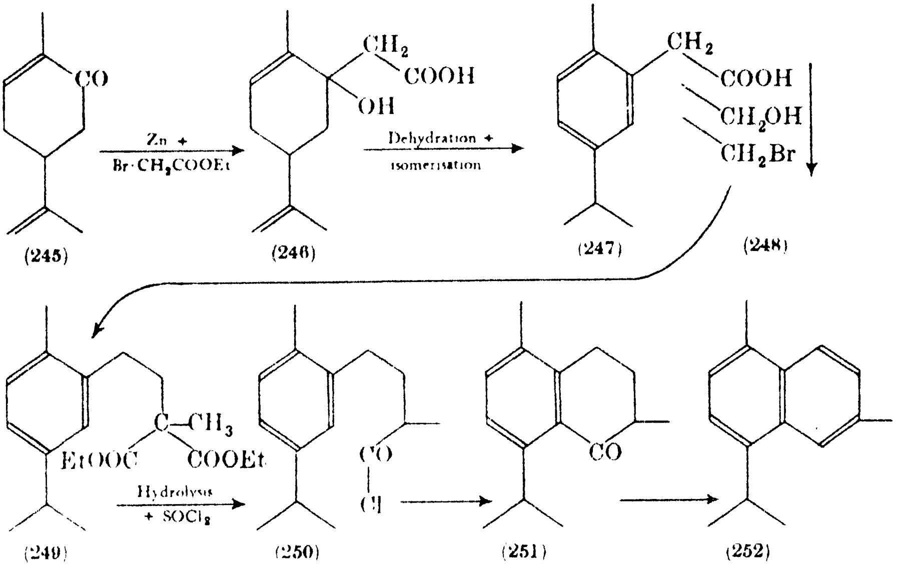
Nerolidol is much more plentiful in natural oils than farnesol, which is prepared commercially by boiling nerolidol with acetic anhydride in a stream of carbon dioxide; both farnesyl and nerolidyl acetates are formed, and after saponification are treated with phthalic anhydride which esterifies the farnesol, but not the nerolidol, which is steamed out and used again. The difarnesylphthalate may be hydrolysed with alkali.

BISABOLOL AND THE CADALENE SERIES

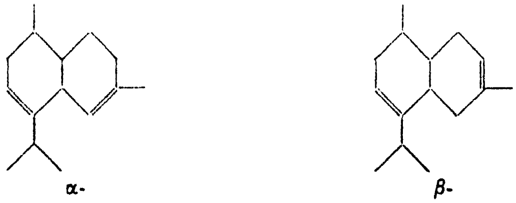
Bisabolene is a pleasant smelling hydrocarbon obtained from oils of lemon, pine and opopanea, and has been synthesised from nerolidol by the following steps. Nerolidol, when converted into farnesol by acetic anhydride produces at the same time some farnesene (239) which, when allowed to stand in acetic acid solution gives bisabolol (240). The latter may be converted by hydrogen chloride to a 'trihydrochloride' (241) and this, by sodium acetate and acetic acid to bisabolene (242). Although there is still some trace of doubt as to the position of the third double bond in bisabolene, no doubts exist as to the structure of bisabolol, which has been synthesised by Ruzicka. The Grignard reagent from 2-methyl-5-bromopentene-2 (243) was allowed to react with the ketone (244) obtained from the oxidation of α-terpineol; bisabolol is thus produced. The direct conversion of nerolidol to bisabolene takes place on boiling with acids.



When the sesquiterpene cadinene is dehydrogenated by sulphur or selenium, cadalene $C_{15}H_{18}$ is obtained. Its chemical properties indicate that it is probably a naphthalene derivative since it will not, in spite of its lack of hydrogen, show addition reactions. The structure of cadalene has been confirmed by synthesis. Carvone (245) with zinc and bromacetic ester readily passes into cymyl acetic acid (247) through the intermediate (246). The acid may be reduced to the alcohol and converted to β-(2-cymyl)ethyl bromide (248). Reacting this bromide with sodio-methyl malonic ester yields an ester (249), the acid from which, when heated, furnishes γ-(2-cymyl)-α-methyl butyric acid, the acid chloride of which is shown in (250). This acid chloride undergoes an internal Friedel-Crafts reaction on treatment with aluminium chloride, giving the ring ketone (251); this was converted to cadalene (252) by reduction with sodium and amyl alcohol to the hydrocarbon and dehydrogenation with sulphur.



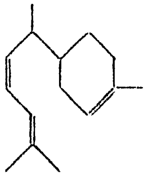
Cadinene $C_{15}H_{23}$ is found in the oils of cade, juniper and cubebs; it is probably a mixture of the α- and β-cadinenes, having the structure below; full confirmation of this structure has yet to be obtained. Two other members of


α- β-

Cadinene

this group which gave cadalene on sulphur dehydrogenation are zingiberene and *iso*zingiberene. Reduction of zingiberene with hydrogen and palladium yields a hexahydro derivative, thus indicating the presence of three double bonds. The arguments for assuming that these double bonds are situated as in formula (253) are derived mainly from considerations of refractive indices.

Zingiberene itself has a molecular refractivity 68·37; the calculated value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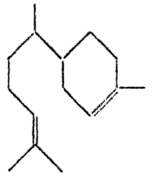
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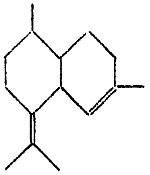
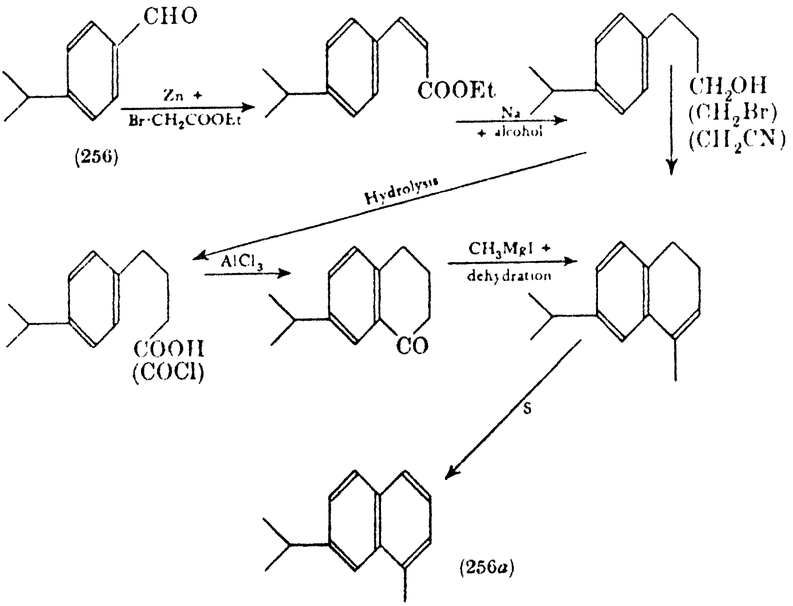

(255)

for a monocyclic sesquiterpene with three double bonds is 67·87, and for an open chain sesquiterpene 69·6. It is therefore probable that zingiberene is a monocyclic sesquiterpene with an enhanced refraction due to conjugation of its double bonds. This is more probable since, on reduction with sodium and alcohol, it yields a dihydrozingiberene with the theoretical molecular refraction of 68·3 ; the structure of dihydrozingiberene is probably (254), indicating conjugation in zingiberene itself. The fact that zingiberene is converted to *iso*-zingiberene by heating with glacial acetic acid containing some sulphuric acid points strongly to the presence of conjugation in zingiberene itself, more especially since *iso*zingiberene has the theoretical molecular refractivity for a dicyclic sesquiterpene with two unconjugated double bonds (255). This is further confirmed by the fact that catalytic hydrogenation of *iso*zingiberene only causes the addition of four hydrogen atoms.

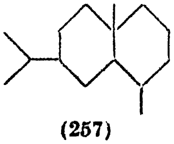
Further confirmation lies in the fact that with dry hydrogen chloride in ether, both zingiberene and *iso*zingiberene give the same hydrochloride, but that on treatment with alcoholic potash, the hydrochloride will regenerate *iso*zingiberene only.

The Eudalene Series

Cadalene is not the only hydrocarbon type from which sesquiterpenes are derived ; many, such as the selinenes, give eudalene on sulphur dehydrogenation. At the same time, however, they yield a molecular proportion of methyl sulphide, an indication of an angular methyl group, which, obviously, cannot be retained by the true naphthalene ring. Thus, eudalene contains one —CH_2 group less than cadalene insofar as its empirical formula is concerned. In 1922, Ruzicka synthesised eudalene (256*a*) from cuminal (256), by the following series of reactions :—

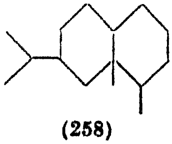


The addition of the angular methyl group to complete the skeleton of the series can be contemplated in two ways to give (257) and (258) ; the former being preferred for a variety of reasons.



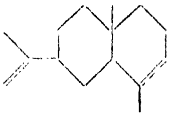
(257)

or

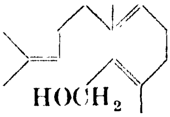


(258)

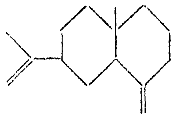
The α- and β-selinenes, the latter of which is to be found in oil of celery seed are derived from the eudalene skeleton by the insertion of two double bonds, the situation of which is very probably as shown in (259) and (260).



α-Selinene
(259)



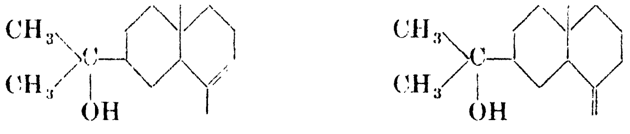
(259a)



β-Selinene
(260)

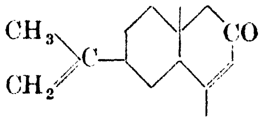
In order to illustrate the relation between the eudalene type of structure and the open-chain sesquiterpenes, farnesol has been rearranged in the formula (259a); it will be seen immediately that the carbon skeletons of the eudesmol and farnesol series are identical.

α- and β-Eudesmol (261), from certain species of eucalyptus, also yield eudalene on dehydrogenation with sulphur and their structure was assigned on grounds of the identity of the dihydrochlorides of eudesmene and selinene. Another closely related substance is the ketonic dicyclic sesquiterpene eremophilone (262), found in the wood-oil of *Eremophila Mitchelli*.



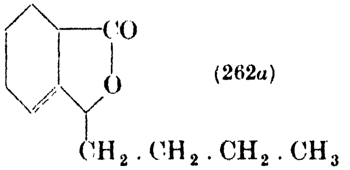
α-Eudesmol β-Eudesmol

(261)

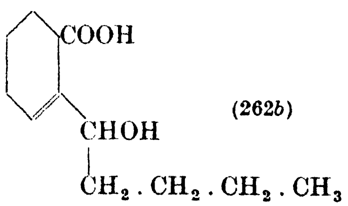


(262)

From the remarks made above, it might be thought that the selinenes were the odoriferous principles of celery. This is not so, the odour being largely due to the lactone sedanolide (262a) derived from sedanolic acid (262b).



(262a)



(262b)

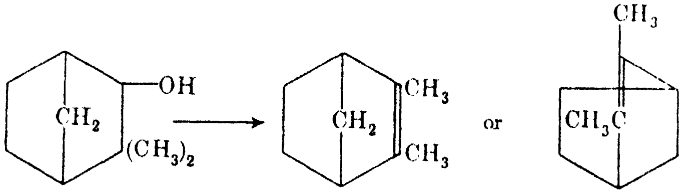
The Tricyclic Sesquiterpenes

There are many tricyclic sesquiterpenes, mainly derived from two series—the α-santalenes and the caryophyllenes. The β-santalenes are dicyclic, but in view of their close relation to the α-santalenes, they will be discussed here.

East Indian Sandalwood contains, among other substances, the following:—

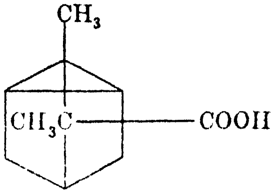
Santene	C_9H_{14}
Santenol	$C_9H_{16}O$
Teresantalol	$C_{10}H_{16}O$
α- and β-Santalene . . .	$C_{15}H_{24}$
α- and β-Santalol . . .	$C_{15}H_{24}O$

Santene (264), 2, 3-dimethyl-1 : 4-*endo*methylenecyclohexene-2, has been synthesised by heating camphenilol (263) with potassium hydrogen sulphate.

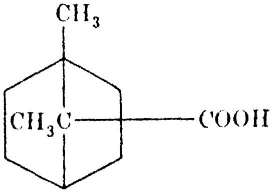


(263) (264)

Santene is related through teresantalic acid to the more complex members of the series. Teresantalic acid has the structure (265) and has, therefore, a

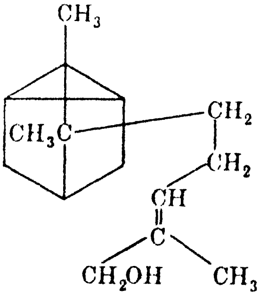


(265)



(266)

camphane structure with a 2 : 6-bridge. This structure was confirmed by conversion to dihydroteresantalic acid (266) by Hasselström in 1931, and by the synthesis of the latter compound. Since teresantalic acid is produced as the oxidation product of both α-santalol and α-santalene, it follows that the residue of the structure of these compounds must be attached through the carbon of



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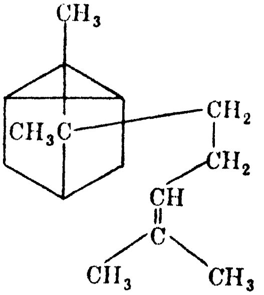
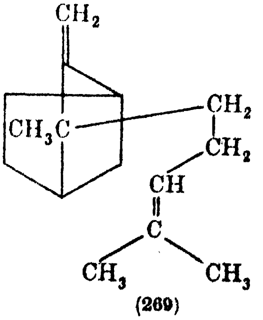
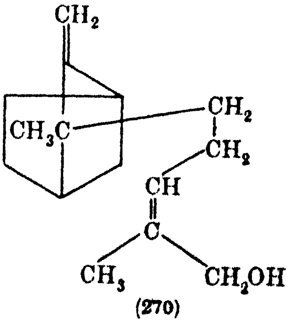


(268)

the carboxyl group of teresantalic acid (267) and (268). The nature of the side-chain has been ascertained by gradual oxidation. β-Santalene and β-santalol are, however, dicyclic, and their structures, concerning which there is still some element of doubt, are probably given by (269) and (270) :—

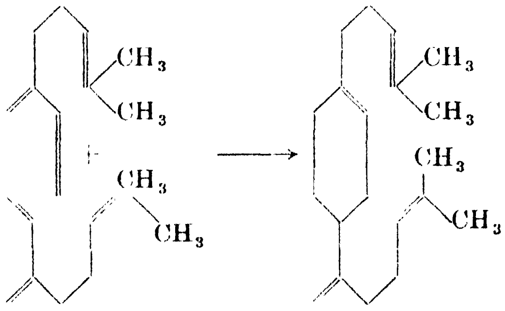


(269)



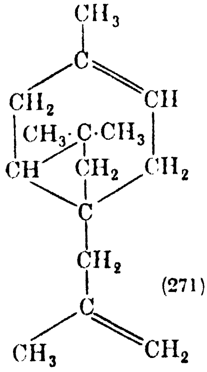
(270)

Camphorene (from oil of camphor) is one of the few C_{20} terpenes the constitution of which has been elucidated. Reference has already been made to myrcene (2-methyl-6-methenyloctadiene-2, 7) (see p. 681) ; myrcene dimerises to camphorene according to the structure indicated below :—



Myrcene Camphorene

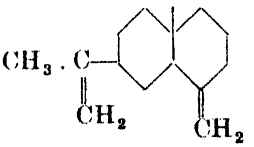
In concluding this consideration of the sesquiterpenes, some mention must be made of the caryophyllenes, although their structure is not known with certainty. Three isomeric caryophyllenes are found in oil of cloves, and as the result of a long series of degradations carried out by Semmler, Simonsen, and others, Ruzicka[1] has proposed the structure (271) for the β-isomeride.



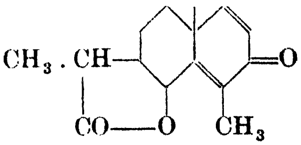
(271)

SANTONIN

Santonin (273) is obtained by extracting the dried unexpanded flowerheads of the worm-seed plant (*Artemisia santonica*) with milk of lime. The solution of calcium santoninate so obtained is worked up for santonin, which is used medicinally as an anthelmintic or vermifuge.



(272)



(273)

When santonin ($C_{15}H_{18}O_3$, m. 170° ; $[\alpha]_D$ − 174° in chloroform) is reduced by Clemmensen's method and the product dehydrogenated with selenium,

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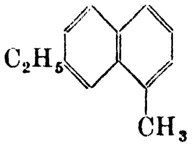
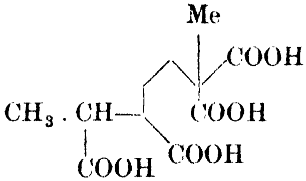
[1] Ruzicka *et al.*, *Helv. Chim. Acta*, **1936, 19, 343.**

1-methyl-7-ethylnaphthalene (274) is obtained, thus bringing the carbon structure of santonin (273) in line with that of the selinenes (272)—the resemblance being

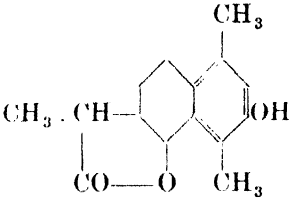


(274)

heightened by the angular methyl group. Evidence of the existence of a methyl group in this position was obtained by Angeli and Mario, who obtained a heptanetetracarboxylic acid (275) by oxidising santonin.

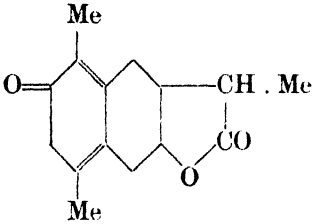


(275)

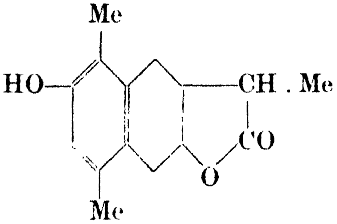


(276)

One of the most puzzling properties of santonin is its conversion by boiling hydrochloric acid into desmotroposantonin (276), which is phenolic, and in which the angular methyl group has altered its position. This change was at first thought to be purely keto-enolic; but subsequent work has not only confirmed the position of the angular methyl group of santonin itself, but has established the formula of desmotroposantonin as (276). As a consequence of this, the formulæ developed by Cannizzaro and his colleagues for santonin and desmotroposantonin were revised (277).



(277)

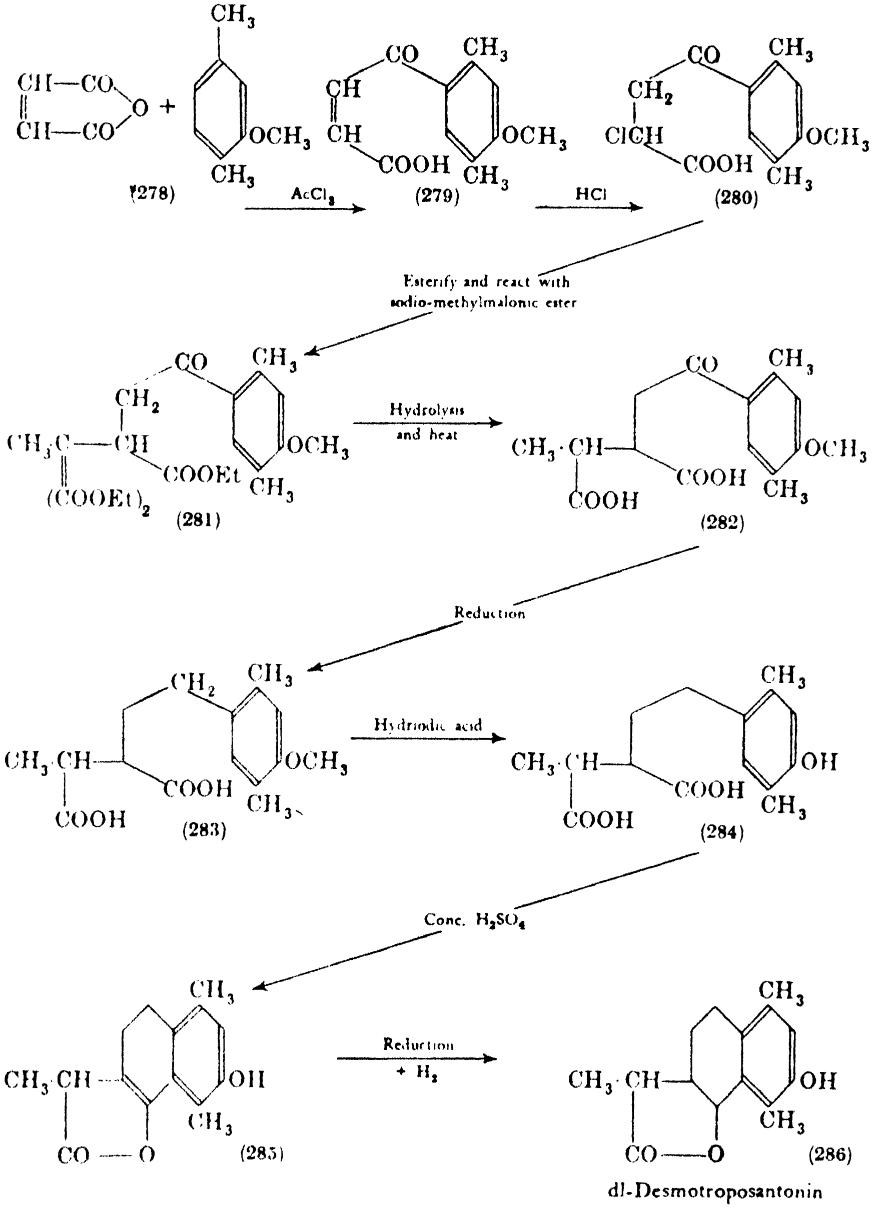


Cannizzaro's formula (now abandoned)

The synthesis of desmotroposantonin by Clemo, Haworth and Walton [1] has put an end to much speculation concerning the exact disposition of the remaining groups. In this synthesis *p*-xylyl methyl ether (278) is condensed with maleic anhydride in the presence of aluminium chloride to give β-(4-methoxy-2, 5-dimethylbenzoyl) acrylic acid (279), the ester of which adds on dry hydrogen chloride, thus producing β-(4-methoxy-2, 5-dimethylbenzoyl)α-chloropropionic ester (280). This compound will react with sodio-methylmalonic ester in the usual manner to give a tricarboxylic ester (281), which on hydrolysis and gentle heating loses carbon dioxide to give α-(4-methoxy-2, 5-dimethylbenzoyl butane-$\beta\gamma$-dicarboxylic acid (282), reducible by Clemmensen's reagent to 1-(4-methoxy-2, 5-dimethylphenyl)pentane-3, 4-dicarboxylic acid (283). The methoxyl of this compound is converted to hydroxyl by Zeisel's method (284). Cyclisation of this acid was effected by strong sulphuric acid, the lactone (285) being isolated, and this, on reduction with sodium amalgam gave dl-desmotroposantonin (286) identical in all respects with that obtained from natural sources.

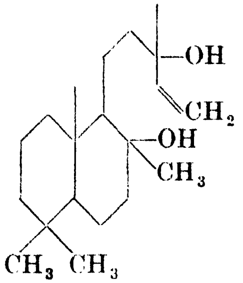
---

[1] Clemo, Haworth and Walton, *J.C.S.*, 1929, 2368; 1930, 1110. Clemo and Haworth, *J.C.S.*, 1930, 2579. Ruzicka, *Helv. Chim. Acta*, 1930, **13**, 1117.

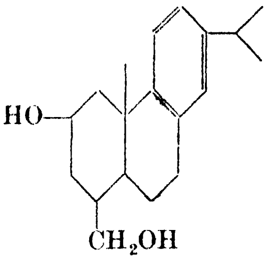


THE POLYTERPENES

Under this heading is included a variety of compounds which have a structural or genetic relation to the simpler terpenes—more especially to the sesquiterpenes just discussed. How close this relation is may be seen by comparing the structure of sclareol (287) and of hinokiol (288), with the structure of the resin acids and carotenoid plant pigments on the one hand, and with the ionylidene compounds on the other.



(287)



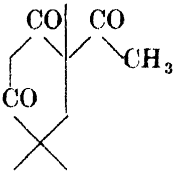
(288)

The substances discussed in this section are divided into the following sections :—

1. Phytol and squalene.
2. Lycopene and the carotenoid plant pigments.
3. Fish pigments.
4. Vitamin A.
5. The resin acids,

whilst consideration of natural and synthetic rubbers, although related to the terpene family, has been discussed in Chapter III.

It is not, perhaps, out of place to emphasise here the persistence of the "ionone" ring in compounds of this series ; even with open-chain compounds such as lycopene and phytol, the ring is potentially present, only needing a simple cyclisation to bring it into being. Even in such compounds as angustione (the β-diketonic compound from *Backhousia angustifolia*) (1, 3, 3-trimethyl-1-acetyl*cyclo*hexandione-4, 6) (289) the ionone ring structure is to be seen.



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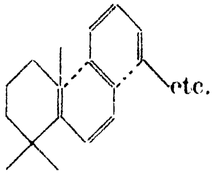


(290)

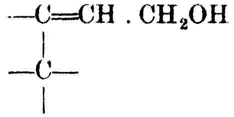
In addition, attention is drawn to the amazing number of instances where the configuration (290) occurs, from which phenanthrene or steroid structures may be obtained by simple cyclisation.

PHYTOL

Study of the structure of chlorophyll has shown it to consist of a complex dicarboxylic acid containing pyrrol rings (see Vol. II), esterified with methyl alcohol and phytol, a complex colourless alcohol of the formula $C_{20}H_{40}O$. General reactions showed phytol to be a primary alcohol and to contain a single double bond ; it can be reduced catalytically to phytanol (dihydrophytol) and to phytane :—

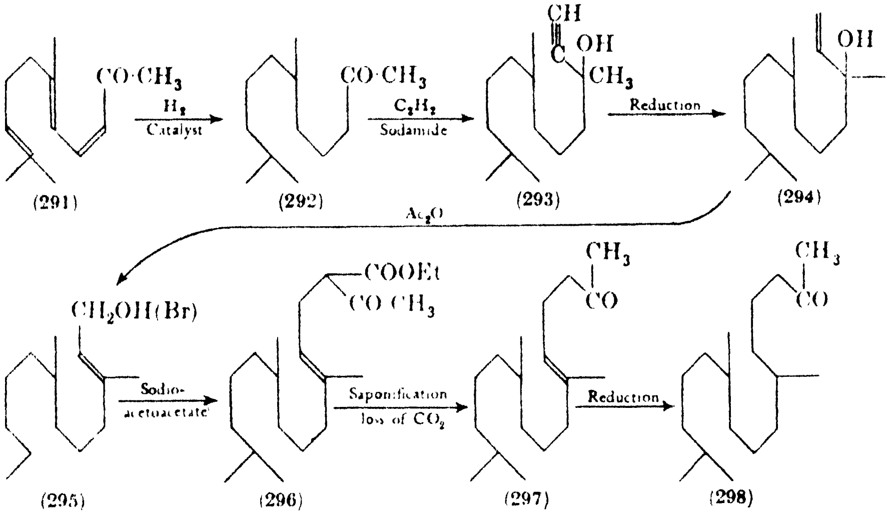
$$\underset{\text{Phytol}}{C_{20}H_{40}O} \longrightarrow \underset{\text{Phytanol}}{C_{20}H_{42}O} \longrightarrow \underset{\text{Phytane}}{C_{20}H_{42}}$$

Oxidative breakdown of phytol gave glycollic aldehyde, $CH_2OH . CHO$, and a ketone, indicating that the double bond is in the position " α " to the primary alcohol group, thus :—



$$\begin{array}{l}—C{=}CH . CH_2OH \\ \quad | \\ —C— \\ \quad | \end{array}$$

The ketone proved to be 2, 6, 10-trimethylpentadecanone-14 (298), the constitution of which was confirmed by synthesis. Commencing from ψ-ionone (291) (*q.v.*), catalytic hydrogenation gives hexahydro*pseudo*ionone (2, 6-dimethyl-



undecanone-10 (292). This ketone reacts normally with sodamide and acetylene to give the corresponding acetylene (2, 6, 10-trimethyldodecyne-11-ol-10) (293). This may be reduced to the corresponding " 11--ene " compound (294), which undergoes on boiling with acetic anhydride the characteristic rearrangement of its class to tetrahydrofarnesol (294). It is to be noted that tertiary alcohols having the configuration

$$>C(OH) . CH{=}CH_2$$

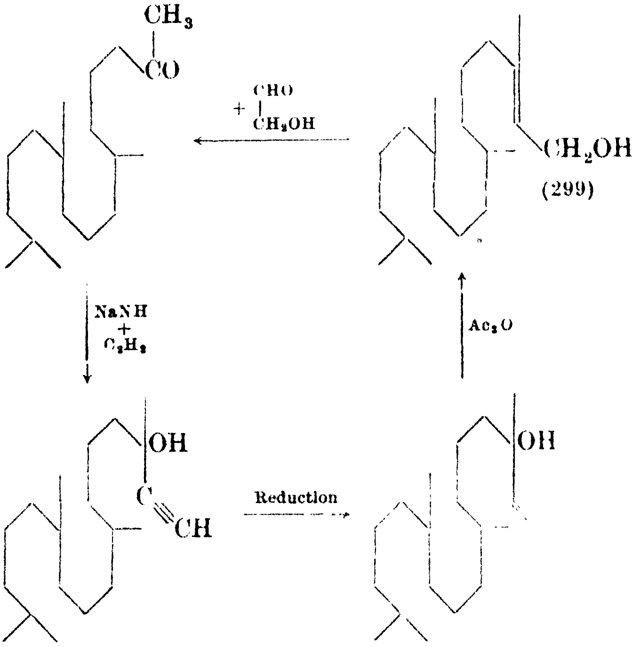
are rearranged by boiling acetic anhydride to

$$>C{=}CH . CH_2OH$$

e.g. Linalool ——→ Geraniol
Nerolidol ——→ Farnesol, etc.

Tetrahydrofarnesol forms the bromide normally, which condenses with sodioacetoacetate to give the compound (296) and regulated hydrolysis leads to the ketone (297), 2, 6, 10-trimethylpentadecene-10-one-14 ; hydrogen and palladised calcium carbonate reduce the double bond without affecting the carbonyl group. 2, 6, 10-Trimethylpentadecanone-14 (298) obtained in this way is in all ways identical with that obtained from phytol, and since the latter is split down into the ketone and glycollic aldehyde, the probable formula for phytol is (299).

This was confirmed by the synthesis of Fischer and Löwenberg,[1] who subjected 2, 6, 10-trimethylpentadecanone-14 to the sodamide and acetylene synthesis (300) in exactly the same way as 2, 6-dimethylundecanone-10, in an



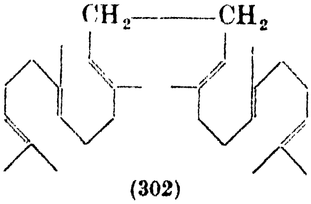
(300) (301)

earlier portion of this series. Reduction and rearrangement of the tertiary alcohol (301) gave phytol identical with that from natural sources.

SQUALENE

Closely allied to phytol, and an important link between animal and vegetable members of this series is squalene,[2] of constant occurrence in the livers of *Selachians* * such as the shark and ray.

Squalene $C_{30}H_{50}$ was for a long time the subject of controversy until Karrer



(302)

suggested in 1930 a symmetrical formula (302) and succeeded, in collaboration with Helfenstein,[3] in synthesising squalene from farnesol (303). The conversion of farnesol to farnesyl bromide (304) gives poor yields, but sufficient bromide can be obtained to give squalene (305) on treatment with magnesium or potassium. Karrer suggested that the natural formation of squalene might take place from farnesol by the condensation (306).

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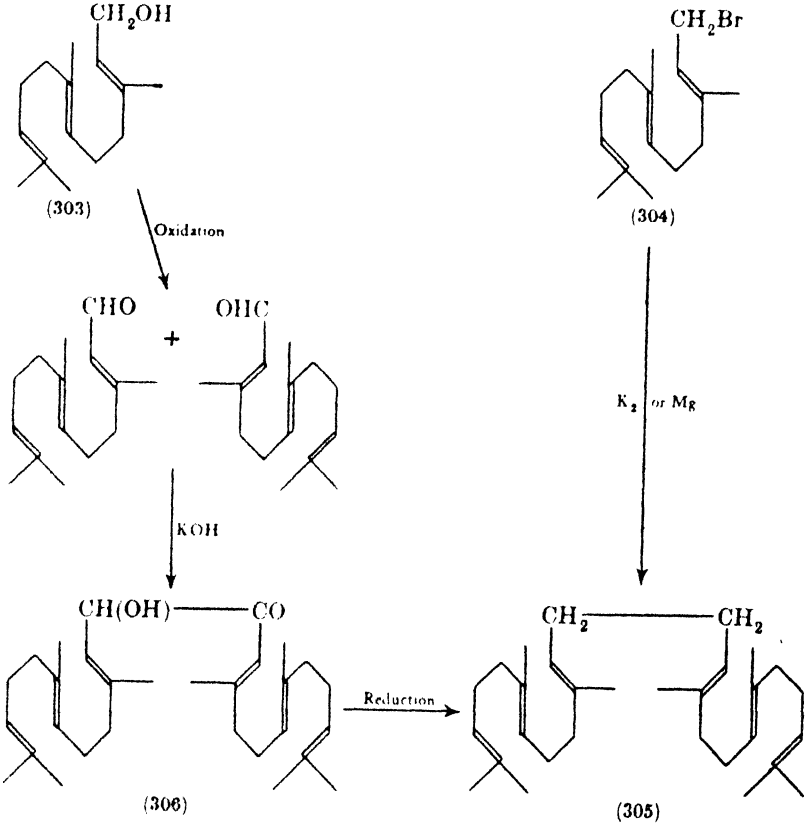
[1] Fischer and Löwenberg, *Ann.*, 1928, **464**, 69 ; 1929, **465**, 183.

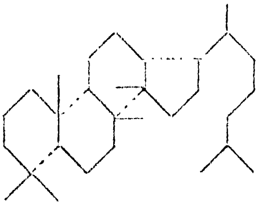
[2] Heilbron *et al.*, *J.C.S.*, 1926, 1630 and 3131 ; 1929, 873.

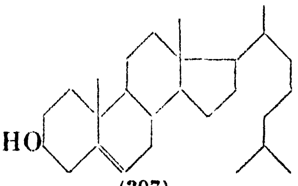
[3] Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78.

* The *Selachians* are considered as a group apart from the fishes (*Pisces*) ; the term "elasmobranch" is often applied to them.



It is of considerable interest to rewrite the carbon skeleton of squalene thus,





(307)

drawing attention to the similarity of its carbon contour to that of the sterols, e.g. cholesterol (307), more especially since the feeding of squalene to rats more than doubles the cholesterol content of the liver. There is a strong probability that demethylation and cyclisation of squalene to sterols takes place in biological reactions and provides at least one link between terpenes and sterols.

The Terpenoid Plant Pigments

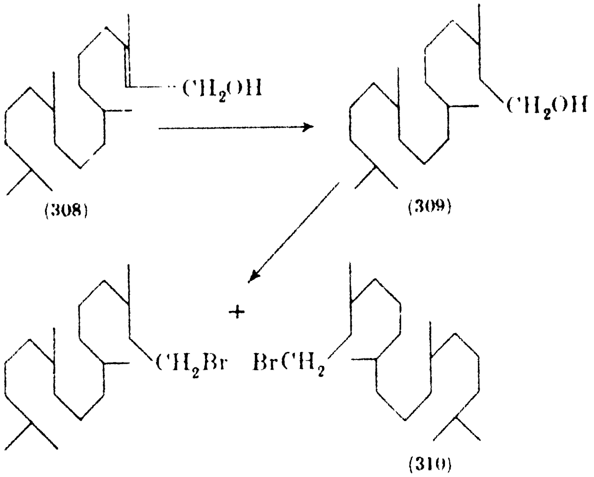
There are a number of red, or orange, plant pigments, the structure of which is closely related to that of the compounds just discussed. It is proposed to discuss the structure of the more important of these pigments here.

LYCOPENE

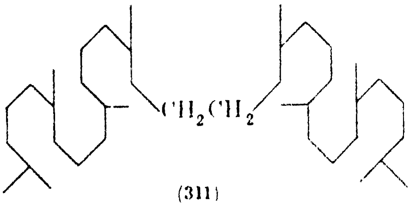
Lycopene $C_{40}H_{56}$, which derives its name from the tomato (*Lycopersicum esculentum*), is widely distributed in nature as a red pigment in rose-hips, bitter-sweet and many similar fruits, being first isolated in 1876.

In the presence of palladised calcium carbonate lycopene adds on thirteen molecules of hydrogen to give perhydrolycopene $C_{40}H_{82}$, thus indicating the presence of thirteen double bonds in the original pigment. The deep colour of lycopene is some indication that many of these double bonds are conjugated.

Perhydrolycopene shows the physical properties of a paraffin, and has been synthesised by Karrer from phytol :—

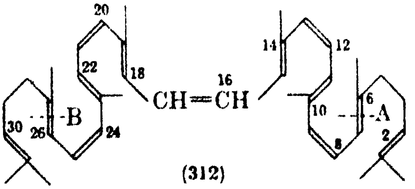


(308) (309) (310)



(311)

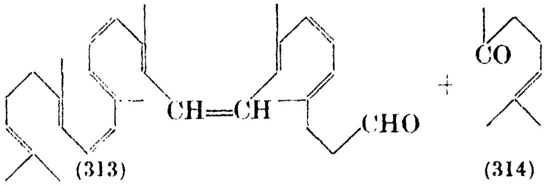
Phytol (308) is readily reduced to dihydrophytol (309), which is converted by concentrated hydrobromic acid to dihydrophytyl bromide (310). Two molecules of the bromide, when acted upon by potassium, undergo a kind of Fittig synthesis to give perhydrolycopene (2, 6, 10, 14, 19, 23, 27, 31-octamethyl-dotriacontane) (311). The carbon skeleton of lycopene is thus made clear and the remaining problem is the positions of the thirteen double bonds. Karrer proposed the formula (312) for lycopene, being guided by its breakdown products, on chromic oxidation.



(312)

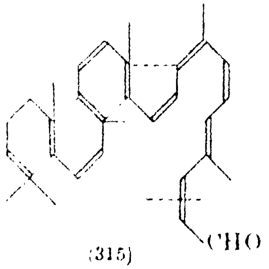
The first break in the structure of lycopene produced by chromic oxidation occurs at A ; the second at B. The formation of methylheptenone (314) and

the aldehyde lycopenal (313) discloses the position of the two double bonds " 2 " and " 6 " and, since lycopene is symmetrical, of the corresponding pair of double bonds at " 26 " and " 30 ".

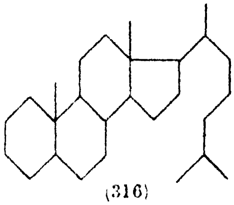


(313) (314)

Lycopenal has a peculiar interest in that it, or its analogues, may be concerned in the biogenetic synthesis of the sterols ; its formula may be rewritten as (315) in which form its resemblance to the characteristic sterol structure (316) becomes

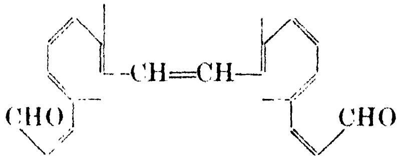


(315)



(316)

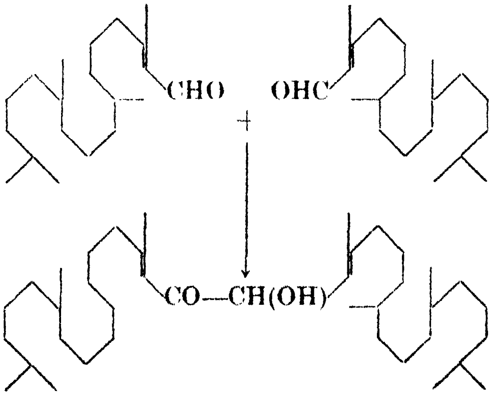
apparent ; ring closure along the dotted lines, demethylation and the fission of a pair of terminal carbon atoms are all that is needed to complete the transformation. The oxidation of lycopenal results in the fission of a second molecule



(317)

of methylheptenone at " B " leaving bixin dialdehyde (317), identical with that produced from bixin itself (*q.v.*). Thus, although no complete synthesis of lycopene is available, its constitutional formula is firmly established as 2, 6, 10, 14, 19, 23, 27, 31-octamethyldotriacontapolyene-2, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30.

Bogert has suggested that the origin of lycopene is through phytolaldehyde, two molecules of which can condense either through a benzoin reaction as shown, or by a pinacone reaction ; reduction and dehydrogenation follows.

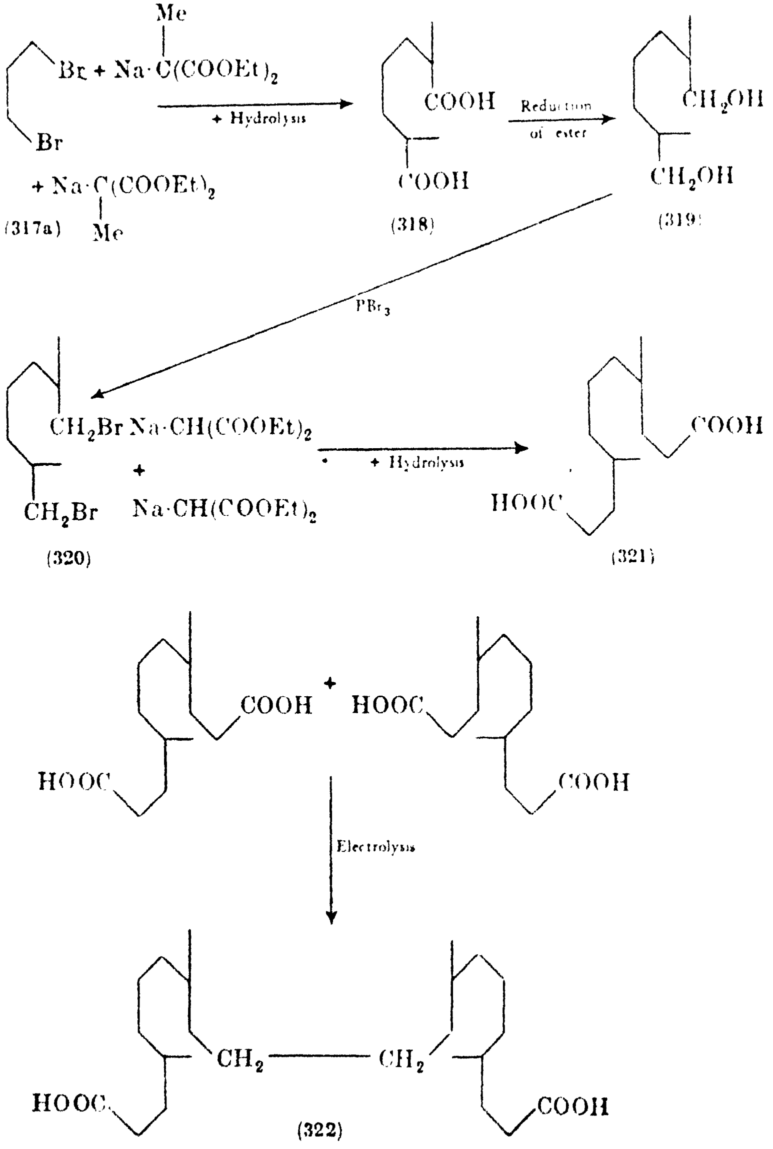


BIXIN AND CROCETIN

Seeds of Annatto (*Bixa orellana*), at one time used for colouring milk, contain a yellow pigment, bixin $C_{25}H_{30}O_4$, which proved to be the monomethyl ester of a dicarboxylic acid ; its formula may be represented :—

$$C_{22}H_{26}\begin{cases}\mathrm{COOH}\\ \mathrm{COOMe}\end{cases}$$

Hydrolysis of the methyl ester yields norbixin, from which the structure of bixin itself has been elucidated. Norbixin can add on nine molecules of hydrogen, this indicating the presence of nine double bonds. The fully reduced compound perhydronorbixin has been synthesised thus :—



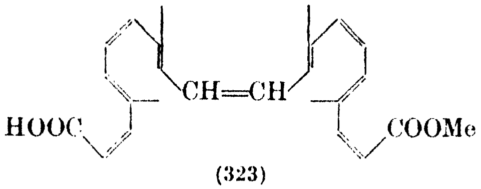
Step I.—1, 3 Dibromopropane (317) is allowed to react with the sodio-methyl malonic ester. Hydrolysis of the reaction product gives 2, 6-dimethylheptane-di-acid-1, 7 (318).

Step II.—The di-acid is esterified and reduced with sodium and alcohol to 2, 6-dimethylheptane-diol-1, 7 (319), and converted by phosphorus tribromide to 2, 6-dimethyl-1, 7-dibromoheptane (320).

Step III.—The dibromo-compound is allowed to react with sodiomalonic ester and the resulting product hydrolysed to 4, 8-dimethylundecane-di-acid-1, 11 (321).

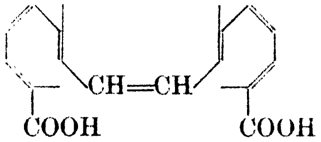
Step IV.—Electrolysis of a solution of the potassium salt of the di-acid yields perhydro-nor-bixin (322) or 4, 8, 13, 17 tetramethyleicosane-di-acid-1, 20 (cf. Kolbe's synthesis).

The position of the double bonds has been arrived at from consideration of the oxidative breakdown of nor-bixin,[1] indicating for bixin itself the formula[2] (323).



(323)

Crocetin, obtained from crocin,* its digentiobioside, the colouring matter of saffron (*Crocus sativus*), $C_{20}H_{24}O_4$ has been formulated[2] (324).



(324)

A number of *cis* and *trans* isomers of bixin and crocetin occur naturally.

THE CAROTENES

In 1831, Wackenroder (of "solution" fame) isolated from carrots a yellow pigment which he called "carotin", a name since changed to "carotene". The three principal carotenes (α, β and γ), are formulated below (325) (326) and (327); they are widely distributed in natural substances, such diverse materials as grass, nettles, carrots, chestnuts and palm oil, all containing appreciable quantities. α- and β-Carotenes ($C_{40}H_{56}$) occur together, and are separated by Tswett's method of chromatographic adsorption,[3] involving the passage of a solution of the mixed pigments in an inert solvent through a column of some material such as alumina or kaolin; the β-form is adsorbed at the top of the

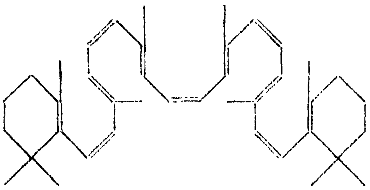
[1] Karrer *et al.*, *Helv. Chim. Acta*, 1932, **15**, 1399; 1933, **16**, 337.

[2] Kuhn *et al.*, *Ber.*, 1931, **64**, 1732; 1932, **65**, 1873.

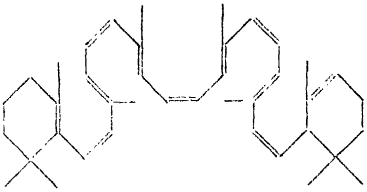
[3] Heilbron, *J.S.C.I.*, 1937, **56**, 160T.

* It has recently been shown that crocin, even in high dilution up to 1 in 10^6, exerts a profound stimulant action on spermatozoa, which probably accounts for the birds' fondness for crocus in spring, and the use of saffron in fertility rites.

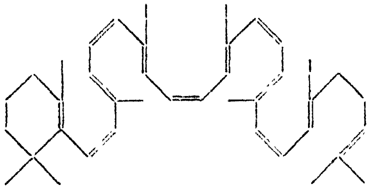
column and the α-form at the bottom, so that by dividing the column, separation is effected.



(325) β-CAROTENE

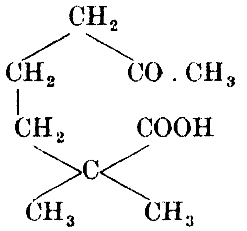


(326) α-CAROTENE



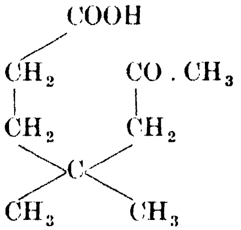
(327) γ-CAROTENE

The constitution of the carotenes has been established by a lengthy series of researches by Karrer,[1] Kuhn [2] and others, mainly through the oxidative breakdown products and by dehydrogenation and cyclisation. The production of geronic acid (328), alone in the case of β-carotene, and mixed with *iso*-geronic



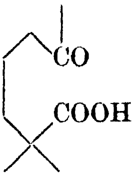
$$\begin{array}{ccc} & CH_2 & \\ CH_2 & & CO\,.\,CH_3 \\ | & & \\ CH_2 & & COOH \\ & C & \\ CH_3 & & CH_3 \end{array}$$

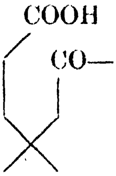
(328)



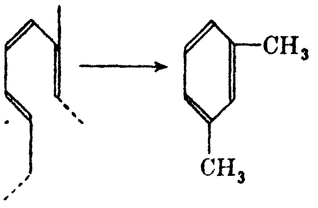
$$\begin{array}{ccc} & COOH & \\ CH_2 & & CO\,.\,CH_3 \\ | & & | \\ CH_2 & & CH_2 \\ & C & \\ CH_3 & & CH_3 \end{array}$$

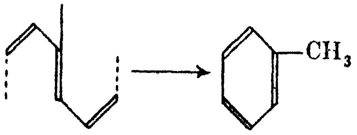
(329)





acid [3] (329) in the case of α-carotene, indicates the nature of the end-components. Thermal degradation of β-carotene gave toluene and *m*-xylene, presumably from cyclisation of fragments of the unsaturated chain joining the two ionone rings thus :—





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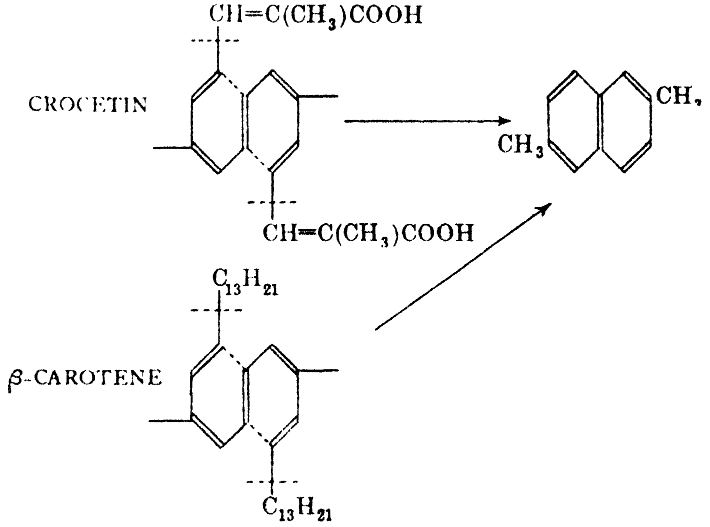
[1] Karrer *et al.*, *Helv. Chem. Acta*, 1930, **13**, 1084 ; 1931, **14**, 1033.
[2] Kuhn *et al.*, *Ann.*, 1935, **516**, 95.
[3] Karrer *et al.*, *Helv. Chim. Acta*, 1931, **14**, 614 and 833 ; 1933, **16**, 975.

The fact, also, that both *trans*-crocetin and β-carotene yield 2 : 6 dimethylnaphthalene on heating demonstrates the identity of the central portions of their poly-ene chains. The cyclisation is assumed to take place thus :—



γ-Carotene can take up twelve molecular proportions of hydrogen (compared with the eleven taken up by α- and β-carotenes) ; its absorption spectrum lies between those of lycopene and β-carotene, and on this, and other grounds, it has been concluded that the structure is made up of one half of β-carotene and one-half of lycopene.

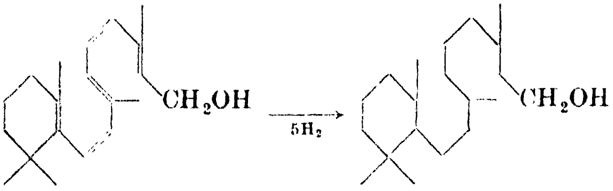
The full story of the oxidative degradation of the carotenes and the identification of the products obtained is too long to be set out in full in a book of this scope ; in general, the results confirm the structures discussed, and for further detail the reader is referred to the selected references at the end of the chapter.

Vitamin A

It is not within the scope of this book to consider the physiological actions of vitamin A ; suffice it to say that it is essential to healthy animal life, and the absence of an adequate supply leads to arrested growth and keratomalacia in growing animals. Early in the study of this vitamin, a connexion was noticed between it and the carotenes ; particularly β-carotene, which appears to be converted into vitamin A in the animal, according to the equation :—

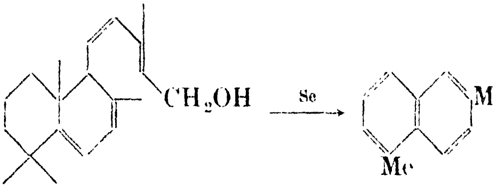
$$C_{40}H_{56} + 2H_2O = 2C_{20}H_{30}O$$

Chemical work on vitamin A (sometimes called 'axerophthol') has been hampered by its great sensitivity to oxidation. Karrer and his co-workers found halibut liver oil to be a rich source of vitamin A, and obtained from it very active preparations ; later from mackerel livers, a preparation was isolated which was considered to be vitamin A, with a small amount of other material ; it was a viscous oil ; further work led to the isolation of a fairly pure vitamin A as pale yellow crystals m. 63–64°. The empirical formula $C_{20}H_{30}O$ and molecular weight (Rast's method) of 320, indicate that its molecule is, as suggested above, half the size of that of carotene. It reacts as a primary alcohol, and by catalytic hydrogenation may be converted to a perhydro compound (341) containing 5 molecules of hydrogen more than vitamin A itself. This points to a polyene structure, and taken together with its known relation to carotene and its production of geronic acid upon oxidation, led Karrer to formulate it thus :—



(340) (341)

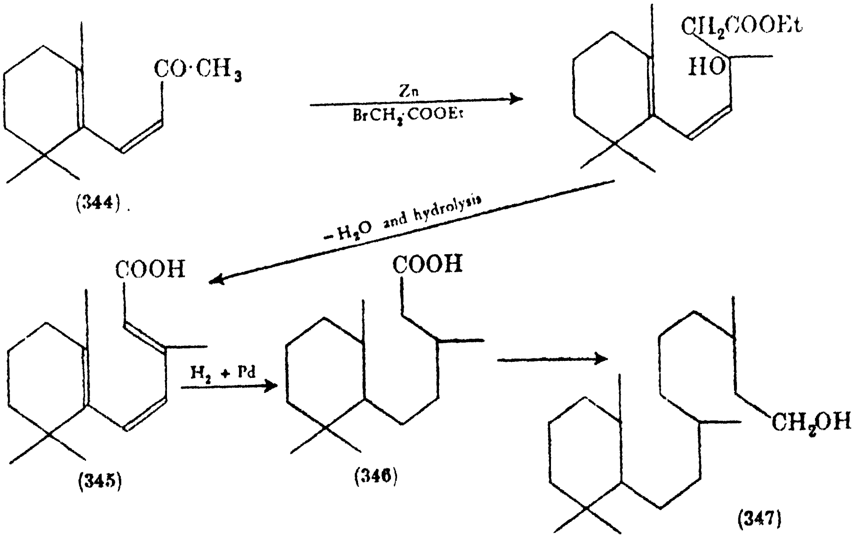
Heilbron and his collaborators have shown that vitamin A is rapidly cyclised by alcoholic hydrogen chloride, the substance obtained being formulated (342).



(342) (343)

Selenium dehydrogenation of this compound gave 1, 6-dimethylnaphthalene (343), thus confirming part of the structure suggested for vitamin A itself.

Karrer [1] confirmed his view of the nature of the carbon skeleton of vitamin A, by synthesis of perhydrovitamin A. β-Ionone (344) was subjected to a Reformatski reaction with zinc and bromoacetic ester, followed by the removal of the hydroxyl group, to give β-ionylidene acetic acid (345). This was reduced to its perhydro compound (346) and by lengthening the chain by a series of reactions along orthodox lines, perhydrovitamin A was obtained (347).



The identity of perhydrovitamin A from natural sources with the synthetic material was established, and two co-workers of Karrer-Kuhn and Morris claim to have synthesised material rich in vitamin A itself.[2] In the many attempts to synthesise vitamin A, one difficulty has been the production of β-ionylidene acetaldehyde ; β-ionylidene acetic acid (345) was obtained in the synthesis of perhydrovitamin A, but on account of its unsaturated structure has proved exceedingly difficult to convert to the aldehyde. Kuhn and Morris attempted to effect this reduction by treating β-ionylidene acetic ester (348) with magnesium methyl iodide and o-toluidine, thus obtaining the o-toluidide (340). This, on treatment with phosphorus pentachloride in benzene solution

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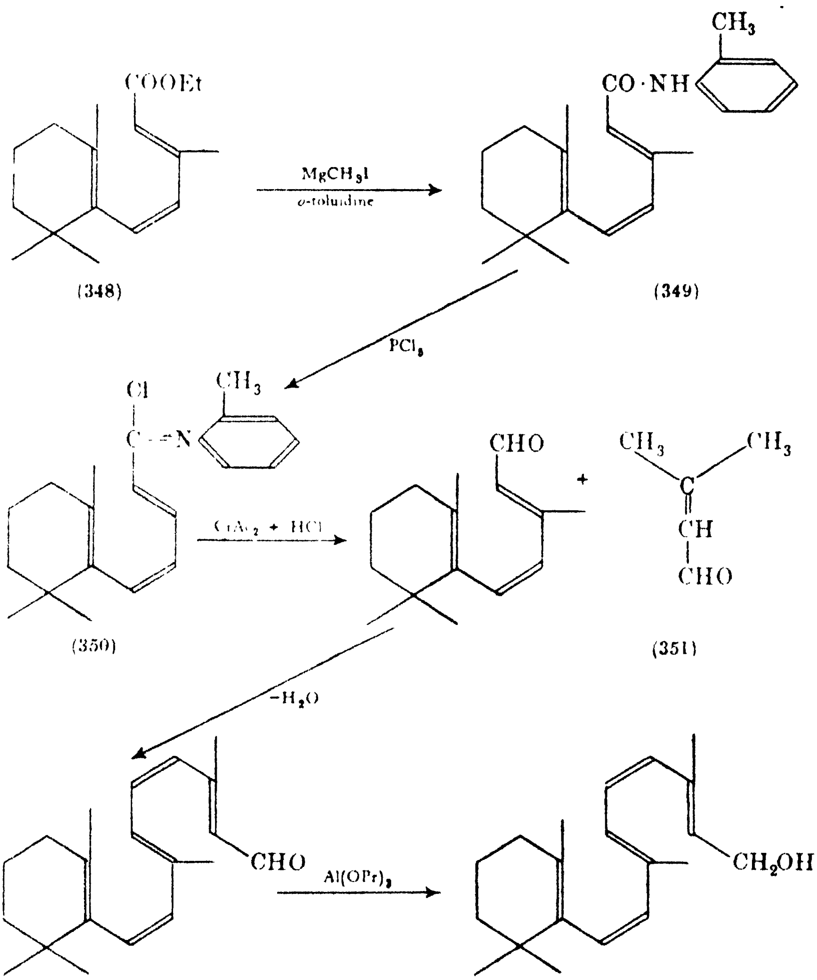
[1] Karrer *et al.*, *Helv. Chim. Acta*, 1931, **14**, 1036 ; 1933, **16**, 557.

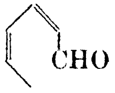
[2] Kuhn and Morris, *Ber.*, 1937, **70**, 853.

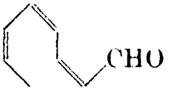


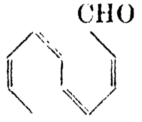
(348) (349) (350) (351) (352) (353)

at 0°, gave the imino chloride (350) which is reduced by chromous acetate in acid solution to the Schiff's base, which, under these conditions, hydrolyses to the aldehyde (351). β-Ionylidene acetaldehyde, a limpid colourless liquid with a terpene-like odour, condenses with β-methylcrotonaldehyde to give the aldehyde corresponding to vitamin A (352). The reduction of so sensitive an aldehyde proved difficult, but finally was carried out successfully with aluminium *iso*-propoxide, $Al(OPr)_3$ (Ponndorf's reagent) (cf. " Avertin ", Vol. II). The final product purified by chromatographic adsorption on alumina had the colour reactions and growth-promoting properties of an impure vitamin A (353), but the crystalline vitamin could not be isolated. Doubts have been cast on the identity of the β-ionylidene acetaldehyde obtained in this series of reactions ; although a crystalline semicarbazone was isolated, it is difficult to exclude the possibility of a structural change having taken place.

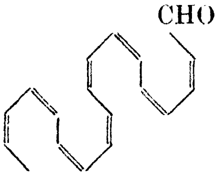
So far, the preparation of pure β-ionylidene acetaldehyde has not been satisfactorily settled ; many attempts have been made to build up polyene-aldehydes from simple substances by auto-condensation. The straightforward unsaturated aldehydes can easily be produced by the condensation of crotonaldehyde and acetaldehyde in the presence of piperidine.[1] The reaction was shown by the earlier investigators to give the three substances :—

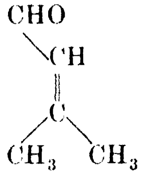

Hexadienal-2, 4.

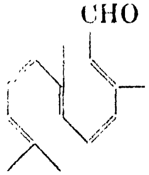

Octatrienal-2, 4, 6.


Decatetraenal-2, 4, 6, 8.

but later work by Schmidt [2] has shown that it is possible to carry the condensation in regular steps to octadecaocta-enal-2, 4, 6, 8, 10, 12, 14, 16 (353*a*)


(353*a*)


(353*b*)


(353*c*)

The later members of this series are orange or deep red, and bear an obvious structural resemblance to the carotene family. By commencing the condensations with β-methylcrotonaldehyde (353*b*) it has been found possible to proceed as far as farnesinal (353*c*), the structure of which is reminiscent of β-ionylidene acetaldehyde.

The relation of vitamin A to carotene is structurally clear ; the formula of β-carotene, if divided into two equal parts and the terminal group converted to —CH_2OH by the addition of the elements of a molecule of water, gives vitamin A. There is abundant biochemical evidence to show that this change actually takes place in the animal system, probably in the liver, and, moreover, the feeding of β-carotene is equivalent in all biochemical aspects to the feeding of vitamin A ; for this reason β-carotene is often referred to as a ' provitamin A '. Provitamin A activity appears to be related specifically to the intact β-ionone ring which must be without an oxygenated substituent ; any alteration of the position of the double bond destroys the activity.

Whilst the molecule of β-carotene has provitamin A activity equivalent to two molecules of vitamin A, α- and γ-carotenes have only about half this activity, as also has kryptoxanthin (3-hydroxy-β-carotene) ; if both rings are hydroxylated as in zeaxanthin (3, 3′-dihydroxy-β-carotene) provitamin A activity disappears completely. In addition, all the hydrogenated vitamin A series from dihydrovitamin A to perhydrovitamin A have been prepared ; all are without vitamin A activity.

A second substance, vitamin A_2, has recently been detected [3] in freshwater fish, but its structural and biological characteristics are not yet known with certainty.

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[1] Reichstein *et al.*, *Helv. Chim. Acta*, 1932, **15**, 261 ; 1074. Fischer and Wiedemann, *Ann.*, 1934, **513**, 251. Kuhn *et al.*, *Ber.*, 1936, **69**, 98.

[2] Schmidt, *Ann.*, 1941, **547**, 285.

[3] Gillam, Heilbron *et al.*, *Biochem. J.*, 1938, **32**, 118.

THE PHYTOXANTHIN PIGMENTS

The term "phytoxanthin" is applied to those members of the carotenoid family of pigments which contain oxygen; the name "xanthophyll", at one time applied to this group, being reserved for a specific substance obtained from the leaves and petals of certain plants. The principal members of this class are shown in Table VII.

TABLE VII

Name of phytoxanthin	Formula	Properties	Source
Astacene (3, 4, 29, 30 tetraketo-β-carotene)	$C_{40}H_{48}O_4$	Violet, metallic needles, m. 265°	Lobsters
Azafrin	$C_{27}H_{52}O_4$	Red prisms, m. 212	Azafran root
Capsanthin	$C_{35}H_{50}O_3$	Long carmine needles, m. 176°	Capsicum
Flavoxanthin (Trihydroxy-α-carotene)	$C_{40}H_{56}O_3$	Golden prisms, m. 184°	Buttercups
Fucoxanthin	$C_{40}H_{56}O_6$	Dark, thick needles, m. 160·5°	Brown algæ
Kryptoxanthin (3-Hydroxy-β-carotene)	$C_{40}H_{56}O$	Violet prisms, m. 169°	*Physalis* species, where its esters occurs
Lutein (xanthophyll)	$C_{40}H_{56}O_2$	Ruby prisms, m. 195°	Leaves, yellow petals, maize, egg-yolk, sunflower
Physalien		Red needles, m. 99°	The dipalmityl ester of zeaxanthin found in *Physalis*. (Chinese Lantern plant)
Rhodoxanthin	$C_{40}H_{50}O_2$	Blue-black leaflets, m. 219°	A deep blue pigment found in yew berries
Rubixanthin	$C_{40}H_{56}O$	Lustrous copper needles, m. 160°	Hips of dog-rose
Taraxanthin		Yellow prisms, m. 185·5°	*Taraxacum* (Dandelion)
Violaxanthin		Red-brown needles, m. 207°	Pansy, laburnum, nettles and horse chestnut leaves
Zeaxanthin		Golden leaflets, m. 214·5°	Egg-yolk and ripe yew berries (*taxus baccata*)

It is not possible, with the space available, to enter into all the considerations which have led to the assignment of constitutions to these substances. Xanthophyll appears to be dihydroxy-α-carotene (354), its perhydro-compound (355) yielding the diketone (356) on oxidation. Zeaxanthin[1] appears to be the corresponding di-hydroxy-β-carotene (357), and kryptoxanthin the mono-hydroxy-β-carotene (358).

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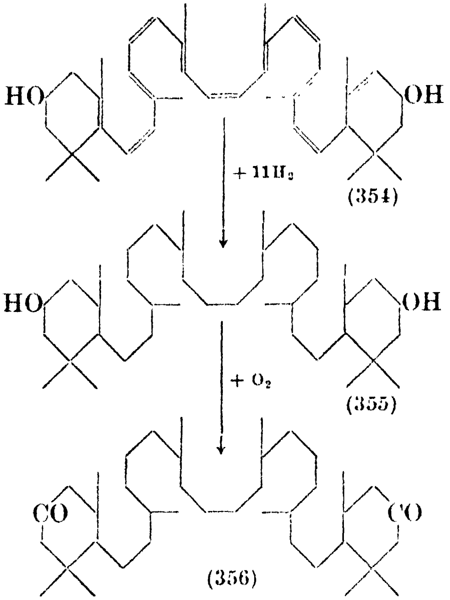
[1] Karrer *et al.*, *Helv. Chim. Acta*, 1930, **13**, 268; 1932, **15**, 490.

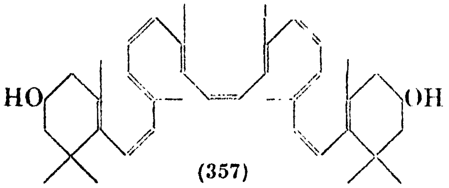


(354)

(355)

(356)

Azafrin,[1] which gives geronic acid on oxidation, and *m*-xylene, *m*-toluic acid and toluene on thermal degradation, has been formulated (359), and rhodoxanthin, the most unsaturated member of this series, is stated to be (360).



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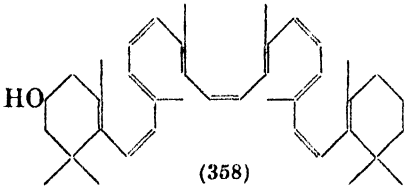

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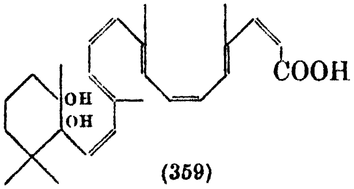

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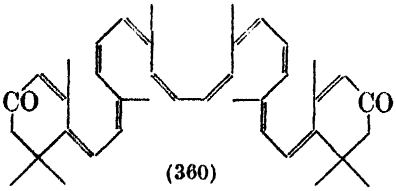

(360)

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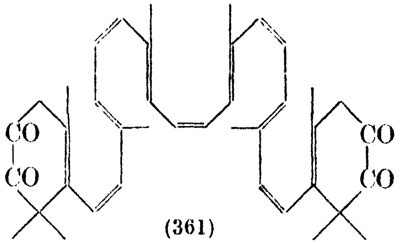
[1] Kuhn and Brodemann, *Ann.*, 1935, **516**, 95.

It is interesting to note that the red colour of the *Crustacæ* (e.g. spider-crab, lobster) of gold-fish, prawns, the liver of the angler-fish, together with the pink of the salmon and the red of the star-fish, are due to a pigment of this series, astacin (from the lobster, *Astacus grammarus*). It is 3, 4, 29, 30, tetra-keto-β-carotene (361).[1]



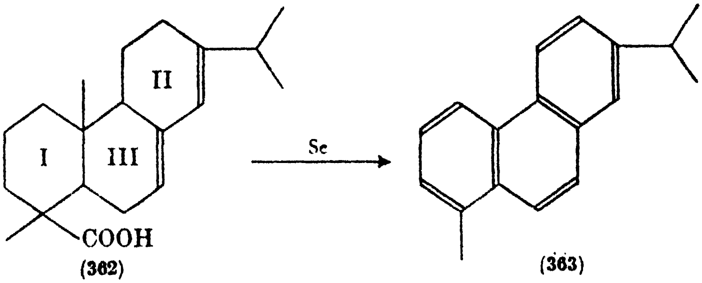
(361)

As this book goes to press, new carotenoids are being discovered in various natural materials, and much evidence is being published which serves to confirm the structures referred to.

Resin Acids

When the exudates from various species of pine-trees are commercially worked for turpentine by steam distillation, a residue remains, non-volatile in steam, which on cooling solidifies to a hard, glass-like mass of resin. Resins from different species of pine differ, but many of them on boiling with 98 per cent. acetic acid give abietic acid, which crystallises on cooling. This acid does not exist preformed either in the original exudate or in the resin, but is produced from the resin acids by isomerisation. This was shown by Ruzicka and Meyer, who distilled the resin in a very high vacuum when a 90 per cent. conversion to abietic acid was attained.

l-Pimaric acid which occurs in certain resins appears to be an isomeric precursor of abietic acid, which may itself be converted into other acids by heat alone. Abietic acid must be regarded as a relatively stable phase in a long chain of isomerisations, the beginning and end of which are at present unknown. This tendency on the part of abietic acid to pass into other compounds has hampered the elucidation of its structure, but reference to its formula (362) indicates its close relation to the polyterpenoid systems already discussed, although in this connexion it must not be assumed that the terpenes themselves are necessarily the precursors of abietic acid (see p. 743).



(362) (363)

Abietic acid, $C_{19}H_{29}$. COOH, gives the hydrocarbon retene (363) $C_{18}H_{18}$, on heating with sulphur or selenium. Since the structure of retene has already been established (363) it may be deduced that the structure of abietic acid contains the 1-methyl-7-*iso*propylphenanthrene group. Ruzicka, in order to determine the fate of the remaining carbon atoms, heated abietic acid with palladised charcoal at 300–330°, obtaining a 90 per cent. yield of retene, together with 4 molecular proportions of hydrogen, one of methane and one of (CO + CO_2). The carbon oxides are from the carboxyl group, the hydrogen from the nucleus, and the methane from a methyl group which must have occupied some special position, since otherwise it would have been retained as is the " 1 "-methyl group. There is a strong presumption that the position occupied must have been an angular one, such groups being known to furnish methane on dehydrogenation thus :—

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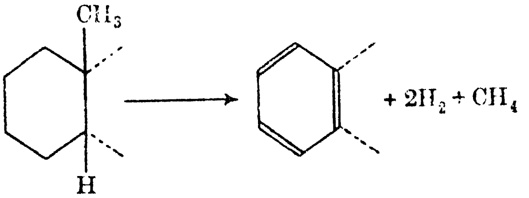
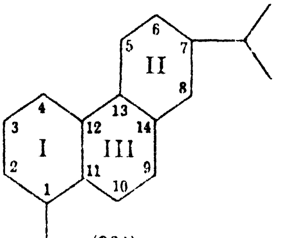
[1] Sorensen, *Tids. Kjemi. Bergvesen*, 1935, **15**, 12. Karrer and Hübner, *Helv. Chem. Acta*, 1936, **19**, 479.



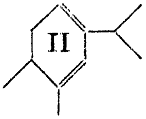
This gives the structure of abietic acid as 1-methyl-7-*iso*propyl decahydrophenanthrene (364) with a methyl group at positions 11, 12, 13 or 14, two double bonds and a carboxyl group in, as yet, unspecified positions.



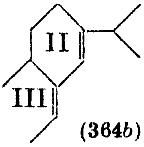
(364)

Evidence concerning the positions of these groups may be summarized as follows :—

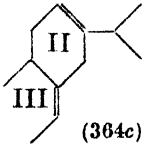
1. The fact that abietic acid gives a Diels-Alder adduct [1] with maleic anhydride was at one time held to confirm the existence of a conjugated diene structure, which was, on somewhat slender premises, assigned to ring II as in (364*a*), whilst the isolation of *iso*butyric acid was regarded as further confirmation. The fact, elicited in 1936,[2] that during the supposed addition, abietic acid was transformed into *l*-pimaric acid which then added to maleic acid, left the position of the double bonds still unsettled.



(364*a*)



(364*b*)



(364*c*)

2. Kraft [3] showed that the absorption spectrum of abietic acid indicated a conjugated diene system and Vocke [4] suggested that the diene structure embraced rings II and III as in (364*b*).

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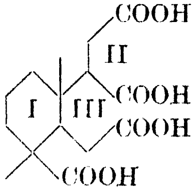
[1] Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 1289.

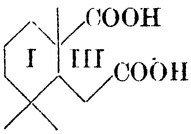
[2] Ruzicka *et al.*, *J.S.C.I.*, 1936, **55**, 546.

[3] Kraft, *Ann.*, 1935, **520**, 138.

[4] Vocke, *ibid.*, 1932, **497**, 247.

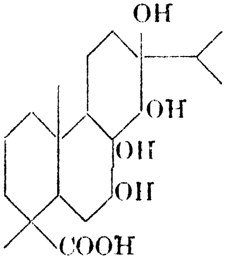
3. Evidence from the permanganate oxidation of abietic acid shows the formation of two acids :—



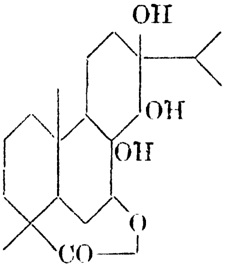


which confirms the fact that the double bond system embraces the two rings II-and III, but does not distinguish between the structures (364*b*) and (364*c*), the latter of which cannot be excluded solely on spectroscopic grounds.

4. Controlled oxidation of abietic acid gives a tetrahydroxy derivative (364*d*) which yields an anhydride (364*e*) ; careful study of the oxidation



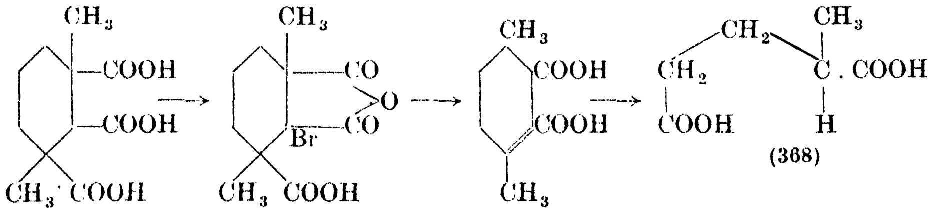
(364*d*)



(364*e*)

products[1] of this lactone indicates that it contains a glycerol structure, and that the three remaining hydroxyls are attached to three adjacent carbon atoms thus confirming the structure of (364*b*) insofar as the double bonds are concerned.

5. Ruzicka isolated from the products of energetic permanganate oxidation of abietic acid, a C_{11}-acid. This acid was subjected to a minute examination by Vocke, who came to the conclusion that it was best represented



(365) (366) (367) (368)

by the formula (365) ; the C_{11}-acid gave the degradation products (366 to 368), but it is clear that other interpretations could be placed on the evidence.

A series of investigations by Ruzicka and others tends to confirm the structure of the C_{11} acid as (365), so that abietic acid is now regarded as having the established formula (369). *d*-Pimaric acid which gives pimanthrene (1, 7-dimethyl retene) on dehydrogenation is regarded as (370).

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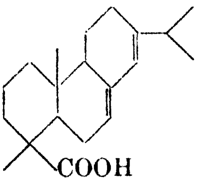
[1] Ruzicka and Sternbach, *Helv. Chim. Acta*, 1941, **24**, 223.



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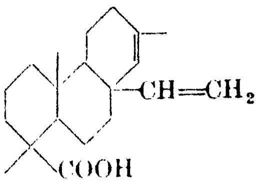


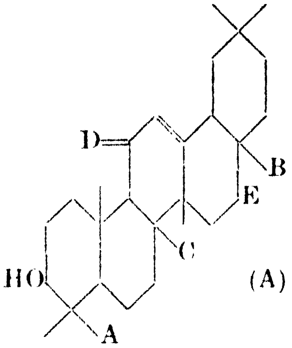
(370)

TABLE VIII.—SOME TRITERPENES

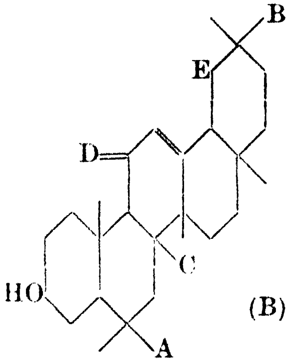
Name	Structure					Source and discovery
	A	B	C	D	E	
β-Amyrin	CH_3	CH_3	CH_3	H_2	H	Discovered by H. Rose in 1839 in elemi resin. H. Rose, *Ann.*, 1839, **32**, 297
Erythrodiol	CH_3	CH_2OH	CH_3	H_2	H	Found with its stearic ester in the fruit of the cocoa-bush. Zimmermann, *Rec. Trav. Chim.*, 1937, **57**, 1200
Oleanolic acid	CH_3	COOH	CH_3	H_2	H	Occurs free in cloves and olives, and as a glycoside in sugar-beet, mistletoe and marigold
α-Boswellic acid	COOH	CH_3	CH_3	H_2	H	
Hederagenin	CH_2OH	COOH	CH_3	H_2	H	From ivy and soap-nuts
Gypsogenin	CHO	COOH	CH_3	H_2	H	From soap-wort (*Saponaria*)
Glycyrrhetic acid	CH_3	CH_3	COOH	=O	H	From the glycoside of liquorice. Ruzicka and Leuenberger, *Helv. Chim. Acta*, 1936, **19**, 1136
Echinocystic acid	CH_3	COOH	CH_3	H_2	OH	
Quillaic acid	CHO	COOH	CH_3	H_2	OH	From the glycosides of quillaia bark used for putting the 'head' on beer
Basseol	a tetracyclic diethenoid					From shea-butter
Betulin	Hydroxylupeol					From birch-bark

TRITERPENES

Various triterpene derivatives have been found in the saponins of plants, such as ivy (*hedera*), liquorice (*glycyrrhiza*), oleander, etc. These saponins are nearly all substituted and hydrogenated derivatives of picene and the two alternative key formulæ for the basic structures are shown below :—



(A)

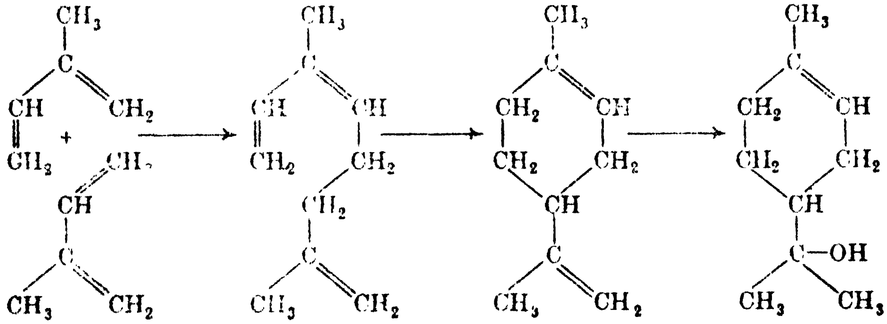


(B)

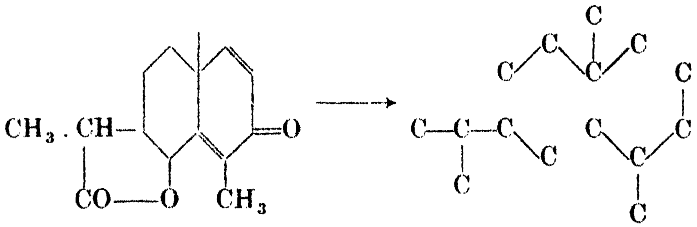
Structure (A) is due to Haworth[1] and (B) to Bilham and Kon.[2] Space does not allow a consideration of the arguments leading up to the establishment of the structures, but those of the various members of the β-amyrin group are indicated in Table VIII on opposite page.

BIOGENESIS OF THE TERPENES

Much speculation has been devoted to possible methods by which terpenes and terpenoid structures are built up in plants. The "isoprene hypothesis," as originally presented, involved the formation of terpenes from two or more isoprene units, followed by such simple hydro-additive or oxidative processes as are known to take place in biological systems ; for example, the monocyclic terpenes could be obtained through dipentene thus :—



Apart from the fact that such a scheme involves asymmetric synthesis, there is the obvious limitation, implicit in this hypothesis, that only such compounds would exist in the terpene family, as could be represented (insofar



(371)

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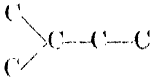
[1] Haworth, *Chem. Soc. Ann. Rep.*, 1937, **34**, 338.   [2] Bilham and Kon, *J.C.S.*, 1941, 552.

as their carbon skeleton is concerned) by an aggregate of isoprene units. Curiously enough, of the vast number of terpene substances known, scarcely any substances have been discovered which violate this condition, and the "isoprene" rule has been invaluable as a " pointer " in probing the structures of terpenes.

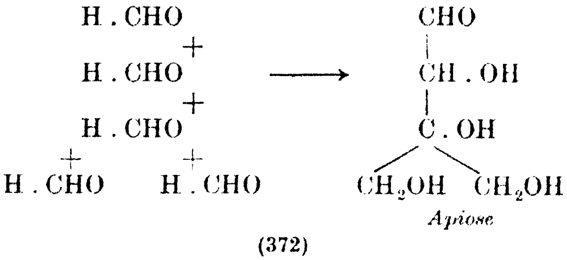
Even such substances as santonin (*q.v.*) may be considered as built up from isoprene units (371). Further, in 1932, Wagner-Jauregg treated isoprene with acetic acid containing a little sulphuric acid and obtained the following terpenes :—

Geraniol
cyclo-Geraniol
Linalool
Terpineol

1, 4 and 1, 8 Cineole and a monocyclic sesquiterpene with three double bonds, transformed by formic acid into a member of the caryophyllene series (see also p. 721).

Useful as the " isoprene hypothesis " has been in assisting in the elucidation of structural problems, it has several serious objections as a practical method of terpene biogenesis. No isoprene has been detected in plants ; the conditions of the Wagner-Jauregg conversion are far more severe than those ever met with in plant tissues ; and finally, even were the preceding difficulties overcome, there is the synthesis of isoprene itself to be considered for which no satisfactory biogenetic method has been advanced. The present tendency is to regard the " isoprene hypothesis " as a convenient formal presentation of the fact that terpenes are built up from an iso-amyl  $\begin{matrix}C\\C\end{matrix}\!\!>C-C-C$ unit, but to withdraw the implication that the biogenetic unit is isoprene itself.

This idea has been partly worked out by Stewart (" Recent Advances ", Vol. II) in which it is pointed out that the natural sugar, apiose, may be considered as built up from five formaldehyde units (372), for which route there is a good deal of independent evidence. Clearly, since apiose has the same carbon

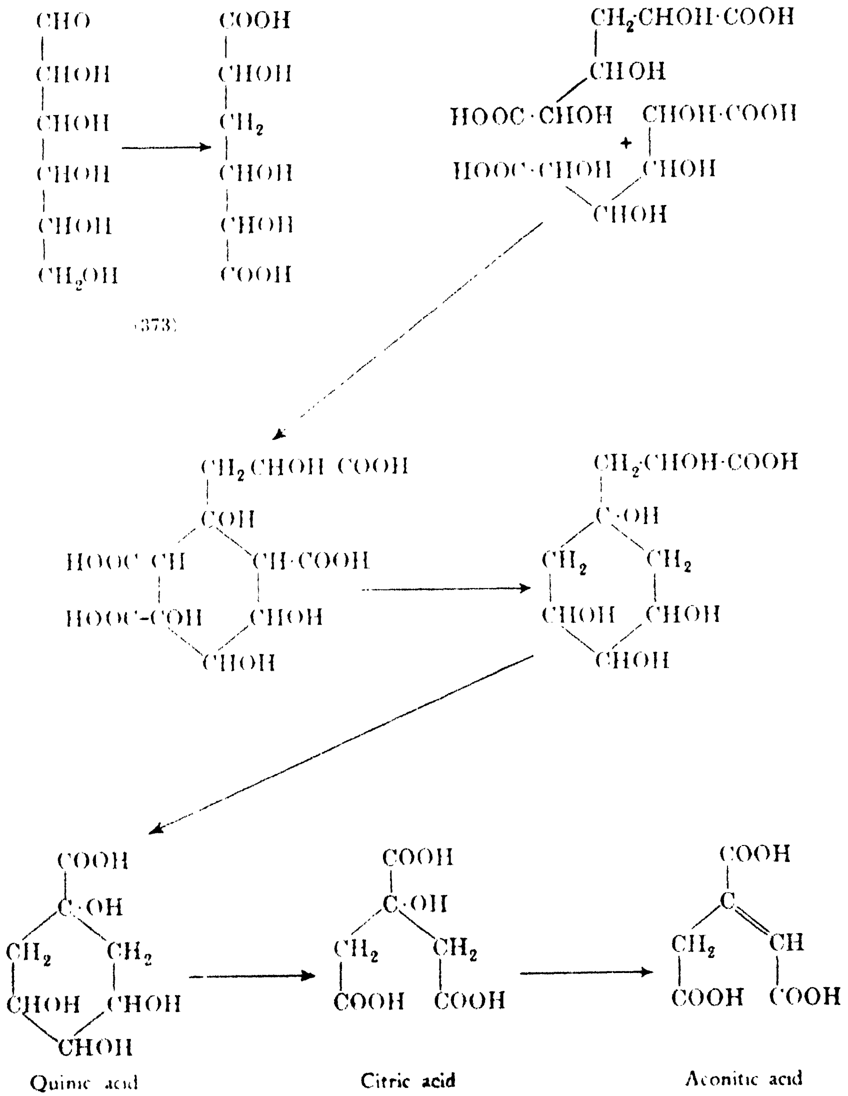


(372)

skeleton as isoprene, the formation of terpenes may equally well be attributed to a continuation of the process of carbohydrate formation in such a way as to involve the condensation of two or more apiose units, followed by reduction. On the other hand, apiose is of comparatively rare occurrence in plants, being found mainly in parsley as a glycoside ; since it is comparatively stable, one would have expected to find it widely distributed if it were the precursor of the terpenoid family.

It has been suggested by Hall that the terpenes may be formed from the carbohydrates, especially glucose through metasaccharonic acid ; the condensation of one molecule of metasaccharonic acid and one of dicarboxylic acid is shown in the scheme shown at top of opposite page.

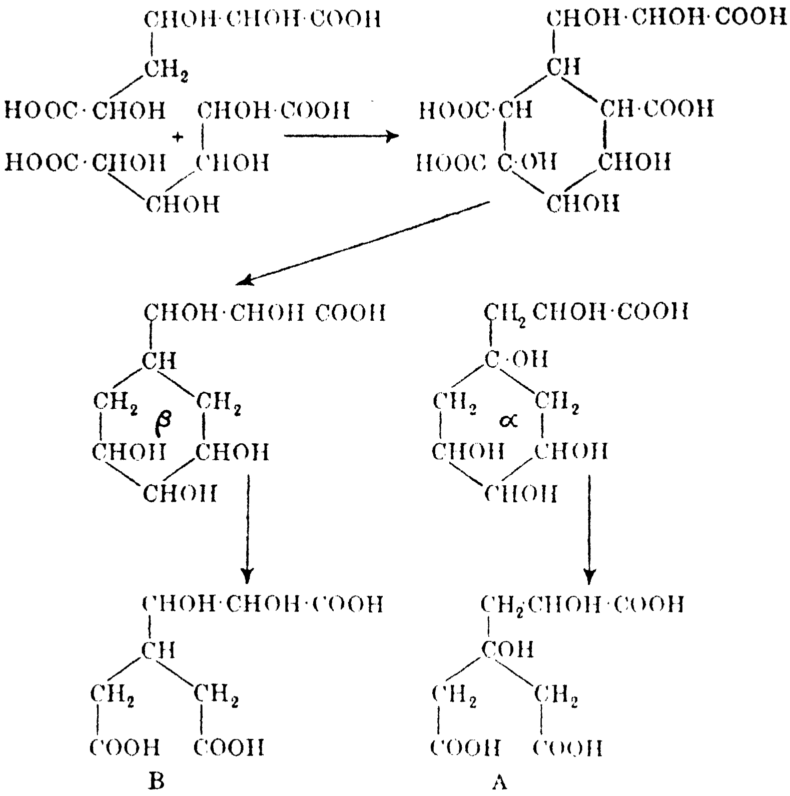
It will be seen that the formation of quinic, citric and aconitic acid could take place along the lines suggested.

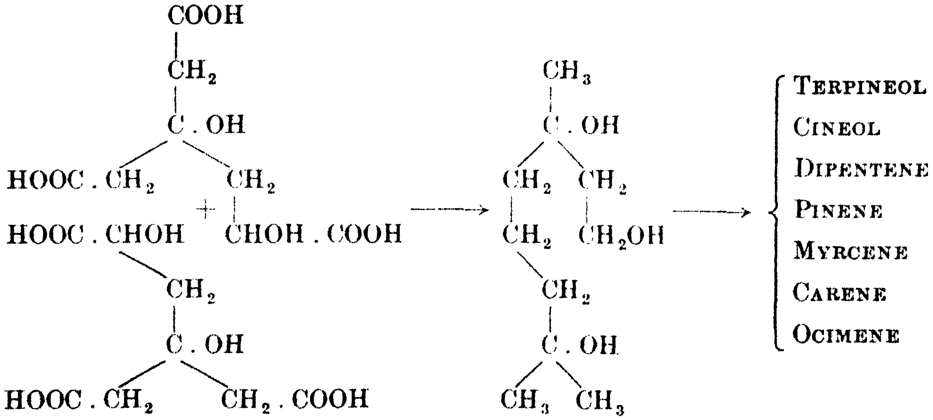


(373)

Alternatively, metasaccharonic acid and the hexosedicarboxylic acid could unite as shown at top of page 746.

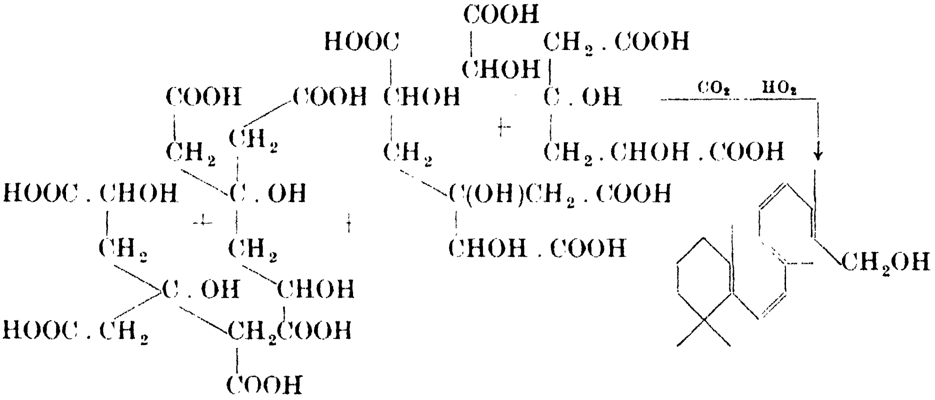
The formation in this way of an acid β, isomeric with the acid α-obtained previously, is merely a preliminary to the formation of the acids A and B. These, according to Hall, are the true precursors of the terpenes, combining in the four possible ways AA ; AB ; BA ; and BB, to give complex acids which lose carbon dioxide with the formation of " terpene-glycerols ", e.g. in the AA condensation, he postulates the formation of the glycerol (374) in the manner shown. The reader will see how extremely simple it would be to form a variety of terpenes from regulated dehydration of this structure.


B
A

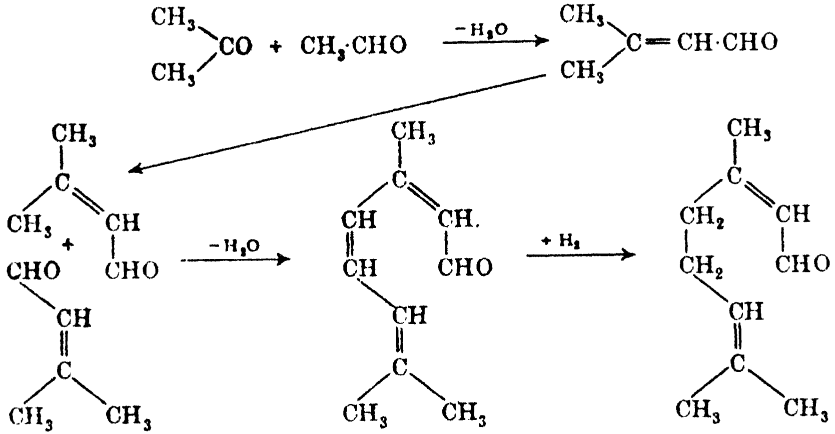

Terpineol
Cineol
Dipentene
Pinene
Myrcene
Carene
Ocimene

(374)

From similar fragments it is possible to build up the structures of more complex substances, such, for example, as vitamin A, or abietic acid. The process for the former is shown below :—



This scheme may contain the germ of the explanation of how terpenoid substances come into being ; at the moment, however, it suffers from being universal ; almost any compound could be obtained (on paper) by taking a sufficient number of "moves", and the theory may be accepted only with reserve ; indeed, until a series of intermediates have been isolated, no biogenetic scheme can be wholly acceptable. Thus, Kremers has suggested the following biogenetic scheme for the terpenes :—



CITRAL

but the isolation of all the intermediates from the natural material has not yet been achieved.

APPENDIX 1

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APPENDIX II

"De gustibus non est disputandum."

ORGANOLEPTIC PROPERTIES OF ORGANIC SUBSTANCES

The impressions we perceive through our senses of smell and taste serve both useful and aesthetic purposes. By means of them mankind can differentiate roughly between good and bad food, between clean and unclean conditions and between normal and abnormal states of health. Aesthetically, smell plays just as important a part in life as colour, although from a physical standpoint we know much less about it. The perfumery industry has arisen from the age-old desire with which man is endowed, to experience the pleasant sensations of smell.

It may be expedient later to divide our consideration of taste and smell into separate sections, but, before doing so, attention must be drawn to a difference in mechanism between the perception of taste and smell, and the perception of colour and sound, namely that physical contact between the substance tasted or smelled and the organ of perception is a prerequisite for perception.

Thus, a substance to be tasted must be placed in the mouth, and an odorous substance must have sufficient volatility for its molecules to vaporise, enter the nostrils, and impinge upon the osmic sensory processes. Since the perceptions of taste and smell overlap to some extent, it is necessary to examine more exactly what processes are involved in the ordinary process of tasting. When food or drink is taken into the mouth the perception of its flavour is composite, and is comprised of four distinct main sensations :—

(1) True sapidity, the effect of the tasted substance on the true organs of taste.
(2) The olfactory sensation or odour, caused by volatile portions of the material ascending into the nose and stimulating the organs of smell.
(3) The tactile sensation.
(4) The thermal sensation.

The tactile sensation is in itself composite, a sensitive tongue and mouth being able to deduce a number of physical characteristics of the tasted substances. The shape of small objects can be roughly differentiated—and the texture, elasticity and colloid nature can be inferred. Examples are the detection by the palate of 'grain' or texture of ice-cream or honey, quite independently of the flavour. a process which is, in effect, an estimate of particle size. Again, the thermal sensation is stimulated independently of the taste or smell ; and, indeed, may be stimulated by means other than variations in temperature. Thus, menthol produces in the mouth a true sensation of cold in the sense that by its effect the thermal sensory nerve endings send an impulse to the brain similar to that which would have been produced by a cold substance. Similarly the pungency of pepper, and ginger, is related closely to the sensation of heat.

It must not be thought that there is an individual mental sorting out of these various impressions during the process of tasting ; the reception of the sensations is covered by an integration factor. Thus, in tasting marmalade the following sensations will be concerned :—

(1) Temperature.
(2) Size, shape, texture and mechanical strength of the peel.
(3) Consistency and texture of the jelly.
(4) The acidity, bitterness and sweetness of the materials.
(5) The pungency of the essential oils.
(6) The olfactory sensations from the essential oils and oleo-resins.

All these are integrated by the brain in the single concept ; of them, only No. 4 is concerned with the taste organs proper ; this factor is often referred to as 'true sapidity'.

TRUE SAPIDITY

The true taste organs—or 'taste-buds' are a series of minute organs distributed over the interior of the mouth, the tongue and the mucous membranes of the upper part of the throat. The statement is often made that they are only capable of differentiating between four distinct tastes :—

(1) The *sweet* taste, as, for example, that of sugar.
(2) The *bitter* taste, as typified by a dilute solution of quinine.
(3) The *sour* taste, as of acids.
(4) The *saline* taste, as of a dilute solution of salt.

Indeed, Skramlik [1] went so far as to say that any true taste sensation could be reproduced by mixing together solutions of sucrose, salt, quinine and tartaric acid ; in addition, Lazarev [2] asserted that the taste-buds are divided into four distinct groups, in accordance with the established fact that different taste sensations are associated with different areas in the mouth. His statements are unsupported by morphological evidence, and it is now fairly certain that no simple theory of taste on the lines just described is adequate.

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[1] Skramlik, *Z. Sinnes-Physiol.*, 1921, **53**, 36.
[2] Lazarev, *J. Russ. Chem. Phys. Soc.*, 1922, **54**, 106.

If an analogy from the world of colour is permissible, it would be as follows: An average non-technical person, asked how many colours he knew, would answer that he was acquainted with some hundreds; a person with some knowledge of elementary physics might supplement his answer by saying that the colours were divisible into four or five groups, the greens, blues, reds, yellows and violets. In the same way, a casual observer might claim that there are hundreds of tastes and a more thoughtful man might claim them to be classified into a few groups on ground of similarity. It does not follow in the case either of colour or of taste, that because a number of sensations fall within the 'yellow' or 'sweet' class, that they are of necessity identical.

The latter statement becomes more apparent when sweet substances are considered in detail. Dilute solutions of saccharin, dulcin and perilla-aldoxime can be made each of which is equivalent in intensity of sweetness to a 5 per cent. solution of sucrose. Such solutions are of equivalent sapidity, but are easy to distinguish one from another; moreover, on mixing any two of them the resultant solution has a higher equivalent sapidity than either solution tasted separately; in short, the three substances do not act on the same group of taste-buds. Careful examination of sapid substances shows them to have five main types of taste:—

(1) Acid.
(2) Bitter.
(3) Sweet.
(4) Saline.
(5) Meaty.

The phenomena of sweetness and the production of artificial sweet substances is dealt with in the Appendix II to Chapter X. The sensation of acidity is associated with the presence of the hydrogen ion, although the anion has also some influence on the general perception of flavour. Thus two acids at dilutions of the same *p*H taste different. Further, there appears to be some other disturbing factor and no linear relationship between *p*H and acid sensation can be detected. Thus, N/800 hydrochloric acid has a just perceptible acid taste; acetic acid at N/200 has only one-quarter the hydrogen ion concentration of N/800 hydrochloric acid, yet tastes strongly acid; and there are several well-known acids—citric, tartaric, malic and the like, in which it is observed that the apparent acidic sapidity is greater than that to be expected from the *p*H of their solutions. This may be due to the lipid nature of the sensory portions of the taste-buds which would tend to extract such acids from their solution to a greater degree than the mineral acids, thus giving a higher apparent sapidity.

The bitter taste is possessed by many organic substances, and it is amongst this family that wide differences in type of taste are experienced. Cohn[1] records several thousand substances of a bitter taste, but these range through the unbearably 'metallic' bitterness of strychnine, through quinine to the pleasant bitters of the grape-fruit.

A fairly detailed description of the problems arising from the 'meat-taste' is given below, partly as an example of the research which has been conducted in this type of field.

Utilisation of chemical products having a meat taste dates back to the earliest times; aspergillus mould fermentation of soya-bean meal to obtain the *shoyu* ("soy") is really a form of production of a crude solution of sodium glutamate. The use of certain species of seaweed, in particular *Laminaria Japonica*, in Japanese cookery, has been customary for centuries, in order to impart a meat-taste. A similar seaweed is also consumed in South Wales coast towns under the name "laver-bread". It is boiled to a pulp and fried with oatmeal.

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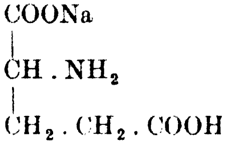
[1] Cohn, 'Die Organischen Geschmacksstoffe', 1914, Berlin.

The use of monosodium glutamate as such (named "*gluta*", "*aji*", "*shuyu*", "*ve-tze-sin*", or more usually "*aji-no-moto*") is mainly due to the researches of Ikeda,[1] who made a series of investigations into the nature of seaweeds which have a meat flavour in order to ascertain to what particular ingredient the unusual flavour is due. He revealed the somewhat surprising fact that the active principle is monosodium glutamate :—



$$\begin{array}{l}\mathrm{COONa}\\ |\\ \mathrm{CH\,.\,NH_2}\\ |\\ \mathrm{CH_2\,.\,CH_2\,.\,COOH}\end{array}$$

which, when in dilute aqueous solution, has a pronounced and strong meat flavour. The curious fact is that neither the free acid, nor its hydrochloride, develop the flavour at all strongly. Again, the remarkable fact emerges that it is only *dextro*-glutamic acid which possesses the strong and characteristic meat taste ; the flavour of the *laevo*-isomer is much weaker and less well-defined ; it was shown quite clearly by Chao-Lun-Tseng and Ju-Hwa-Chu[2] that the synthetic *dl*-product is not the complete sapid equivalent of the natural *d*-isomer. The same investigators[3] also examined a long series of glutamic mono-salts, and found that only the salts of sodium, potassium and methylamine ($CH_3 . NH_2$) showed the meat taste, and of these, the two last-named developed a peculiar brackish after-taste.

Their investigations[4] were also extended to a consideration of which carboxyl group was neutralised in the monosodium salt, and they concluded that the carboxyl group adjacent to the —$CH . NH_2$ group was the one concerned.

The meat flavour of monosodium glutamate is still perceptible even at one part in 3000 of water ; since sucrose has a threshold sapidity of one part in 300 of water, this figure is a fairly high one. The Chinese and Japanese use the mono-sodium salt mixed with a little common salt as a condiment, and for flavouring rice and other cereal dishes. It is interesting in this connexion to note that the ancient Japanese used to add, for the purpose of meat flavouring, the powdered flesh of a certain dried fish ; it has been shown by Ikeda that this material is rich in sodium glutamate. The use of the "*aji-no-moto*" (*literally*, the "principle of taste") is widespread ; and a strong contributory factor to the use of this condiment is the fact that Buddhists disapprove of a meat diet ; the "*aji-no-moto*" is approved and allowed ; it forms a welcome addition to, and dispels the monotony of an exclusively cereal diet.

A mono-sodium glutamate (with salt) preparation is now manufactured in this country ; some is imported from Holland, mainly for the production of imitation soup-powders.

Peng-Cheng-Hsu and Adolph,[5] as the result of a long series of animal experiments, concluded that the use of sodium glutamate has no adverse action on the course of digestion and assimilation from the alimentary tract.

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[1] Ikeda, *Eighth Internat. Congr. App. Chem.*, **18**, 147.

[2] Chao-Lun-Tseng and Ju-Hwa-Chu, *Acad. Sinica. Res. Inst. Chem.*, 1937, No. 5, 1.

[3] Chao-Lun-Tseng and Ju-Hwa-Chu, *J. Chinese Chem. Soc.*, 1933, **1**, 188.

[4] Chao-Lun-Tseng and Ju-Hwa-Chu, *Science Quarterly*, Pekin, 1932, **3**, 1.

[5] Peng-Cheng-Hsu and Adolph, *J. Chinese Chem. Soc.*, 1936, **4**, 42.

There are a number of other substances which owe part of their flavour to the presence of mono-sodium glutamate. It has been shown by Monti[1] that tomato sauce prepared in the normal manner contains up to 1·5 gm. per litre of monosodium glutamate, and Dyson[2] was able to isolate the same substance from the shoyu, or matured soy-bean sauce of the East. The soya bean contains a high proportion of proteins of the edestin and zein type, which are rich in glutamic acid units, and the latter are released during the mould fermentation; the appearance, therefore, of sodium glutamate in the fermented material is to be expected.

The production of a strong meat-flavoured soya-sauce is a considerable industry in the Orient—visitors being impressed not only by the large scale upon which the business is carried out, but also by the long time (up to two years) required for the production of the fully matured product. Two raw materials are used; the soya bean itself, which is a buff-coloured oval bean rich in protein and oil, and comparatively poor in carbohydrates when measured against ordinary cereal standards. The balance of carbohydrate is made up by the addition of wheat which has been roasted to incipient brownness and crushed between rolls so that each grain is broken into five or six pieces.

The first operation is the production of immature "*shoyu*" (*shoyu-koji*). The soya beans are soaked in running water for 12 hours to swell and soften them; running water is essential unless sterile materials can be used, since in still water a rod-like organism (similar to *B. mesantericus*) may develop, and leads to an "off-flavour"; running water prevents this growth. The soaked matter is cooked with pressure steam (15 lb. per sq. in.) and all water is blown off from the bottom of the cooker, leaving the beans just moist; they should cool out of contact with the air.

When cooled, the beans are mixed with seven-eighths of their volume of crushed wheat. Much of the success of future operations depends on the skill with which this portion of the operations is carried out. The aim is to coat each bean with an even layer of crushed wheat so that the coated beans move freely over one another without sticking. A loose mixture with plenty of æration channels is essential to prevent uneven attack and overheating in the subsequent moulding; anything in the nature of a pulped mass must be avoided. The function of the crushed wheat, however, is not only mechanical; it gives the colour to the final product and contributes very materially to its flavour.

The next stage in the preparation is the moulding of the prepared material. The moulds used (*Aspergillus flavus* and/or *oryzœ*) are kept as pure culture under laboratory conditions. They are then inoculated into steam sterilised, half-softened rice, and allowed to ripen in an incubator room until sporulation has set in. This bulk-culture, called "tane-koji", has the usual yellow-green wrinkled appearance of a mildew growth; it is mixed with the prepared bean and wheat mixture and the mixture is placed in shallow wooden trays to a depth of 1½–2 inches. Deeper layers lead to overheating; the trays are piled one on top of another in special rooms kept at 24–25° C., and the progress of the moulding is carefully watched by experts.

After 18 hours, each bean has become coated with a silky growth, which is the white mycelium of the mould; there should be no tinge of yellow or green, which would indicate premature sporulation. The contents of the trays are stirred with a thin wooden spatula to effect thorough mixing and transferred for 8 hours to a warmer room (30° C.), after which the mycelia have grown sufficiently long to bind the grains together; another gentle stirring separates them, and they are all left undisturbed for 40 hours, by which time their temperature will have risen to 35–36° C. The mass is now a green colour, since sporulation has set in and all the interstices between the beans are filled with mycelium, consolidating the contents of each tray into a mass. The temperature during this latter stage must not exceed the value given or else the flavour of the product suffers.

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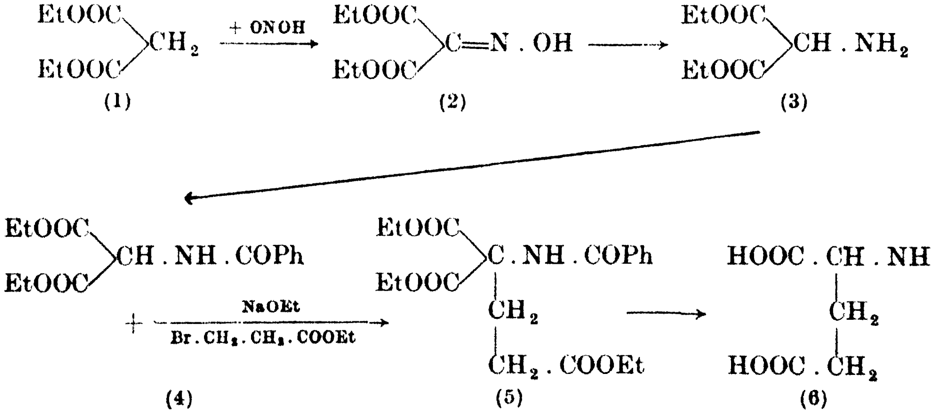
[1] Monti, *Staz. Sperimentale. agrar. Ital.*, **44**, 813.

[2] Dyson, *Pharm. J.*, **1928**, **375**.

The trays are carefully inspected for signs of the growth of any other moulds. A trace of *Mucor* or *Rhizopus* is ignored, but any considerable growth leads to a bitter flavour ; trays so contaminated are used for preparation of a lower quality "*shoyu*". The "*shoyu-koji*" is now converted to the mature mash or "*moromi*" by stirring the contents of the trays into vats of brine followed by inoculation with the "*shoyu*"-yeast (a species of *Zygosaccharomyces*). The tubs stand in the open, being protected from dust and excessive rain by gigantic straw-hats, conical in shape. After 6 months, much of the solid matter has disintegrated or gone into solution, and the various proteolytic and other enzymes have entirely altered the nature of the material. At the end of the 6-month period the sauce—or "shoyu", as it is now termed—is ready for bottling ; in many cases only a portion is bottled at this stage, the "vintage" material being obtained after 18 months to 2 years. It is a brown, thickish liquid with a pronounced meat-flavour. The curd remaining at the base of the vat is sold at a low price, and is esteemed of considerable value for the feeding of children.

The various chemical syntheses of glutamic acid which have been devised from time to time are ill adapted to the industrial production of that substance. One of the most satisfactory syntheses is that of Dunn, Smart, Redemann and Brown.[1] Malonic ester (1) is converted to its iso-nitroso compound (2), and this is reduced by aluminium amalgam to aminomalonic ester (3).



The benzoyl derivative (4) of this amine is treated with sodium ethoxide and β-bromopropionic ester, producing a complex compound (5), which, on boiling with hydrochloric acid, is hydrolysed to glutamic acid (6). The conversion of glutamic acid to the mono-sodium salt is almost invariably carried out by solution in sodium bi-carbonate solution followed by evaporation.

The process of Keimatsu and Sugasawa [2] is more adapted for use on a large scale. Acrolein (7) is treated with an alcoholic solution of hydrogen chloride, producing β-chloropropionacetal (8), which reacts normally with potassium cyanide to give β-cyanopropionacetal (9). Hydrolysis of the latter yields the half aldehyde of succinic acid (10), which, on treatment (Strecker's method) with ammonia and a cyanide, yields glutamic nitrile (11). Hydrolysis to glutamic acid may then be carried out in the usual way.

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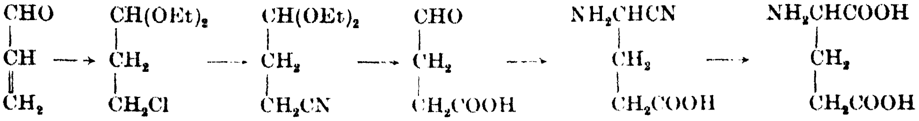
[1] Dunn, Smart, Redemann and Brown, *J. Biol. Chem.*, 1931, **94**, 599.

[2] Keimatsu and Sugasawa, *J. Pharm. Soc. Japan*, 1925, **531**, 369.

The sodium glutamate of commerce is entirely prepared from natural proteins. Several types of raw material can be used ; the original process of Ikeda used seaweed, but this has been discarded in favour of soya-bean, fish-meal or wheat gluten. Yamamoto introduced a fish-meal process for sodium glutamate 20 years ago ; a hydrochloric acid hydrolysis was used on one-half of the material and an alkaline hydrolysis on the other half. On uniting the two portions and concentrating, a mixture of sodium chloride, sodium glutamate and other substances separated. This was claimed by the inventor to contain esters of glutamic acid, which gave the product a superior flavour. The difficulty lies in obtaining an odourless fish-meal as a raw material.



$$\begin{array}{cccccccccccc} CHO & & CH(OEt)_2 & & CH(OEt)_2 & & CHO & & NH_2CHCN & & NH_2CHCOOH \\ | & & | & & | & & | & & | & & | \\ CH & \longrightarrow & CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_2 \\ \| & & | & & | & & | & & | & & | \\ CH_2 & & CH_2Cl & & CH_2CN & & CH_2COOH & & CH_2COOH & & CH_2COOH \\ (7) & & (8) & & (9) & & (10) & & (11) & & (12) \end{array}$$

Ikeda and Suzuki cited wheat gluten and soya-bean meal as the best materials for making monosodium glutamate, the hydrolysis being carried out with hydrochloric or sulphuric acids. The shortage of wheat gluten in the East is due mainly to the very small proportion of gluten in Chinese wheat and to the fact that their demand for starch is small, rendering it unprofitable to extract the gluten. In passing, it may be mentioned that the annual value of imported and home-produced *aji-no-moto* in China is about £380,000. In general, the processes used concentrate on the use of soya-bean meal from which the oil has been removed by pressure and solvent extraction. Takayama [1] describes a process by which the meal is hydrolysed by 50 per cent. sulphuric acid and the glutamic acid separated from the residue as the dibasic calcium salt. Conversion to the monosodium salt may be carried out by double decomposition with sodium carbonate.

Where wheat kernels are available, the Chinese extract starch and oil and grind the kernels to a coarse powder. This constitutes the crude gluten, which is mixed with concentrated hydrochloric acid in coarse earthenware pots (like giant ginger-jars), each fitted with a reflux condenser. Hot oil is circulated round the pots and the true boiling is not allowed to start until the solid matter is all in solution, after which the whole is boiled briskly until a sample withdrawn and diluted fails to give the biuret reaction (absence of protein). On cooling, dark crystals of glutamic acid hydrochloride separate, and may be washed and converted to the sodium salt.

The greatest difficulty is in the purification of the product from the dark-coloured impurities and from arsenic and iron, which comes from the crude glaze of the pots. The process used by Wu [2] in the *aji-no-moto* factory at Tsien Chu is to add a small amount of metallic tin to the charge in the pots, together with a very close temperature control. The tin not only prevents the destruction of the derived material, thereby lessening the amount of dark products, but also, through the aid of nascent hydrogen, removes the arsenic. The final isolation is made by adding alcohol to the partially neutralised and clarified liquor when a white sodium glutamate separates. Details of a laboratory equivalent of this process are given by King.[3]

Takayama's process has certain industrial potentialities which may become valuable ; [4] beet sugar residues are fermented and the alcohol distilled out.

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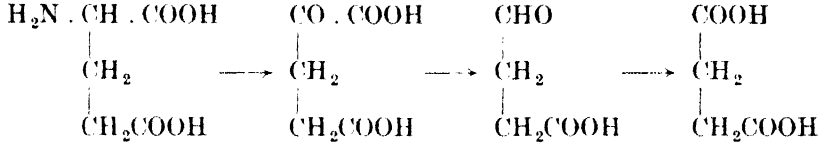
[1] Takayama, *J. Soc. Chem. Ind. Japan*, 1930–1, **33**, 91.
[2] Wu, B. Patent 258655, Sept., 1926.
[3] King, " Organic Syntheses," Coll., Vol. I, 281.
[4] Larrowe-Suzuki, Fr. Pat. 724750 ; B. Pat. 385054 ; and U.S.A. Pat. 1947563.

The residual liquor is dialysed and the dialysate is concentrated; potassium salts and betaine hydrochloride separate and are purified; the mother liquor is concentrated further and the pH adjusted to 3·2, when glutamic acid hydrochloride separates. Ikeda's[1] modification of the Larrowe method described above is widely worked in practice. The *schlempe* (beet residues) is diluted and hydrolysed with hydrochloric acid, as in the original process, but the liquid is then filtered and neutralised with lime; decolorisation with decolorising carbon leaves a liquor which, on evaporation and cooling, deposits calcium glutamate.

One curious source of glutamic acid is the liquor obtained in Foreman's method of peat hydrolysis. Miller and Robinson were able[2] to isolate glutamic acid from this source in fair quantity. It may also be mentioned that glutamic acid is the source of the succinic acid which arises in the fermentation of cereal washes; fermentative process breaks it down in the following way:—



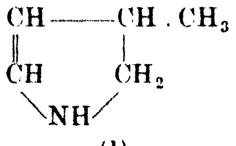
$$\begin{array}{c} H_2N.CH.COOH \\ | \\ CH_2 \\ | \\ CH_2COOH \end{array} \longrightarrow \begin{array}{c} CO.COOH \\ | \\ CH_2 \\ | \\ CH_2COOH \end{array} \longrightarrow \begin{array}{c} CHO \\ | \\ CH_2 \\ | \\ CH_2COOH \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ CH_2COOH \end{array}$$

PUNGENCY

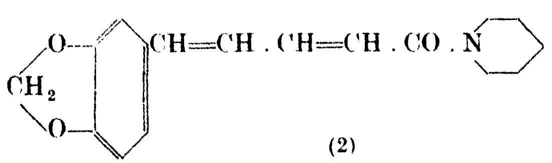
It is doubtful whether pungency—the 'hot'-taste is a true sapidity, since it affects the heat sensitive nerve terminals rather than the taste-buds. It has, however, been the subject of much interesting research, some of which is summarised below:—

This type of pungency must not be confused with the pungency which is associated with easily volatile substances such as the simple mustard oils which are capable of giving sufficient vapour to develop a lachrymatory action. Even so, some of these volatile oils have a pungent action on the sensitive nerves of the mouth in addition.

The Peppers.—The flavour and pungency of pepper (*Piper nigrum*) depends on several factors. Thus Pictet and Pictet[3] showed that black pepper contains a quantity of the alkaloid β-methylpyrroline (1)—but it is doubtful whether this has any connexion with the pungency; its presence may, however, account in part for the difference in flavour shown between the black and white peppers, which are often the fruit of the same plant taken at different seasons of maturity and prepared by different processes.



(1)



(2)

The extent to which the pungency of pepper is due to piperine (2) has been the subject of argument; pepper contains 2–8 per cent. of piperine, but the pungency associated with this compound is only slight when compared with the bulk of the material from which it is prepared. The pungency appears to be associated with the "oleo-resin" portion of pepper which is, in all probability, derived from piperine. Thus, if pure piperine is ground in a mill with flour, the mixture is not pungent until grinding has been carried on for many hours.

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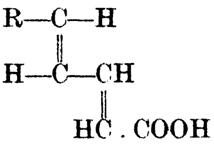
[1] Ikeda, B. Pat. 248453, 1926; U.S.A. Pat. 1928840, 1932.

[2] Miller and Robinson, *Soil Science*, 1921 **11**, 457.

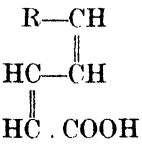
[3] Pictet and Pictet, *H. Chim. Acta*, 1927, **10**, 593.

This may be due to the exposure, during powdering, of a much larger active surface of piperine, or to the formation of a more pungent oxidation product. Piperine is present in several isomeric forms ; thus Ott and Eichler[1] separated chavicin from pepper as previously described by Buchheim[2] and by hydrolysis have isolated a number of acids which appear to be geometrical isomers of piperic acid. It is clear that there are four such arrangements possible :—



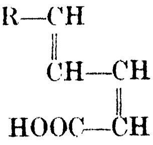
trans-trans

I



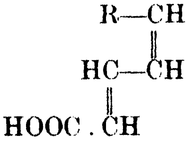
cis-cis

II



trans-cis

III



cis-trans

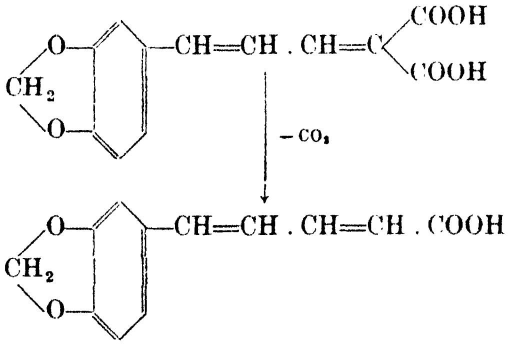
IV

Ott and Eichler associate these structures with the following compounds :—

I. Normal piperic acid, m.p. 217°.

II. Chavicinic acid, the piperidide of which is present as a pungent constituent of black pepper.

III. *iso*-Piperic acid (m.p. 145°), synthesised by the elimination of carbon dioxide from piperonylidene malonic acid :—



IV. *iso*-Chavinic acid, m.p. 200–202° C.

In an attempt to obtain substances of a pungency comparable with that of pepper, Asano and Kanematsu[3] prepared the piperidides of the acids from C_8–C_{14}. Their results are shown in Table IX below :—

TABLE IX

Acid	Carbon No. of acid	Pungency of piperidide
Caprylic .	8	+ + +
Pelargonic .	9	+ + +
Nonylenic .	9*	+ + +
Capric . .	10	+
Undecylic .	11	+
Undecylenic	11*	+
Lauric .	12	
Myristic .	14	

* With one unsaturated link.

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[1] Ott and Eichler, *Ber.*, 1922, **55B**, 2653.

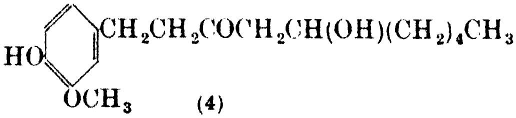
[2] Buchheim, *Arch. exp. Path. Pharm.*, 1876, **5**, 455.

[3] Asano and Kanematsu, *J. Pharm. Soc. Japan*, 1926, 375.

Staudinger and Schneider [1] complemented this work by examination of the piperidides of acids containing fewer carbon atoms. Simple aliphatic and aromatic piperidides had only a feeble pungency, but *n*-valeryl and the alpha, beta and gamma pentenyl piperidides were fully pungent.

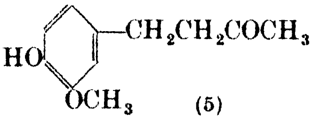
Ginger.—The use of ginger as a spice or condiment dates from the earliest times of which records are available. Ginger itself is the underground stem or rhizome of *Zingiber officinalis*, a reed-like plant.

The ginger of commerce is the dried stem which is often bleached or whitewashed in order to give it a light colour. Its main constituents are starch and fibre together with a volatile oil, to which its odour is due and several constituents on which its pungency depends. These latter were formerly termed the "pungent oleoresin" of ginger, mainly because the pungent principles were extracted together with resinous matters by ether. Investigation has shown that the pungency is in reality due to two principles—gingerol and shogaol, but early work was complicated by the fact that gingerol is readily decomposed into zingerone, a pungent ketone and heptaldehyde. Lapworth, Pearson and Royle,[2] in continuing an investigation of Garnett and Grier,[3] showed that gingerol, the pungent oleoresin of ginger, was capable of decomposition into a ketone zingerone and *n*-heptaldehyde and concluded that gingerol must have the formula (4)

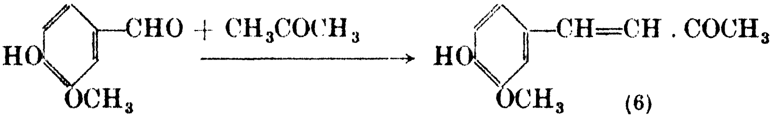


(4)

They isolated and also synthesised zingerone by methods similar to those of Nomura,[4] who had isolated from ginger a ketone, zingerone, which proved to be 1-(3-methoxy-4-hydroxyphenyl) butanone-3 (5) synthesised from vanillin and acetone in alkaline solution (6).



(5)



(6)

The unsaturated compound is reduced to zingerone by hydrogen in the presence of platinum (U.S. *Pat.* 1,263,796 (1918)). Lapworth states that the reduction of 1-(4-hydroxy-3-methoxyphenyl)-butene-1-one-3 to zingerone gives a poor yield, but Nomura claims over 75 per cent.

Nomura and Tsurumi [5] have prepared several homologues of zingerone—in which the terminal methyl group of the side-chain has been increased in length up to nine carbon atoms. No gain in pungency is recorded.

Nomura and Hotta [6] have synthesised a number of reduction products of zingerone and related compounds in an attempt to obtain more pungent compounds and to elucidate the relations between pungency and chemical constitution. Reduction of zingerone gave 1-(4-hydroxy-3-methoxy-phenyl)-butanol-3

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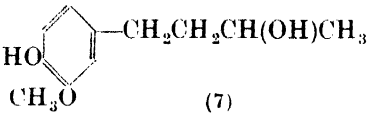
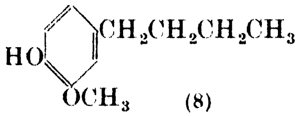
[1] Staudinger and Schneider, *Ber.*, 1923, **56**, 699.
[2] Lapworth, Pearson and Royle, *J.C.S.*, 1917, **111**, 777.
[3] Garnett and Grier, *Pharm. J.*, 1907, **25**, 118.
[4] Nomura, *Sci. Rep. Tok. Imp. Univ.*, 1917, **6**, 41.
[5] Nomura and Tsurumi, *ibid.*, 1927, **16**, 565.
[6] Nomura and Hotta, *ibid.*, 1925, **14**, 119.

(7), and more energetic reduction provided 1-(4-hydroxy-3-methoxyphenyl)-butane (8), both of which have a pungent taste similar to that of zingerone


(7)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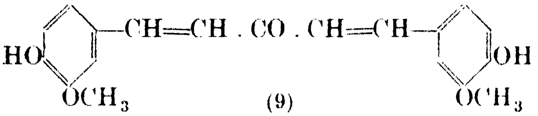
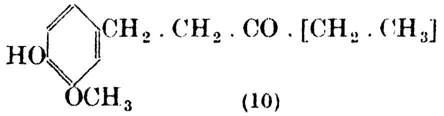
itself. There is, however, a somewhat disagreeable "chemical" flavour observable with these two compounds. These compounds are comparable in many ways with those examined by Marui (*q.v.*).

It is interesting to note that "doubling" of the zingerone molecule produces a series of compounds in which the pungent taste is absent. This is a remarkable confirmation or extension of the observations made in other branches of chemical physiology that the "doubling" of active molecules destroys their activity. Thus, neither disulphonal nor diveronal have narcotic activity. The "doubling" of zingerone was carried out by condensing acetone and vanillin


(9)

to give 1, 5-di(4-hydroxy-3-methoxyphenyl)pentadiene-1,4-one-3 (9) and reducing this with palladium and hydrogen to the corresponding pentanone which is almost tasteless.

Various homologues of zingerone have been synthesised by Ichikawa,[1] Nomura and Seinosuke[2] and Murai[3] e.g. 1-(4-hydroxy-3-methoxyphenyl)-pentanone-3 (10) the corresponding dimethoxy compound and the series of compounds similar to (10) in which the group [ ] is propyl, butyl, *iso*-butyl and *ter*-butyl; in all cases the compounds were strongly pungent. Even the extension of the side-chain to eight carbon atoms as in 1-(4-hydroxy-3-methoxyphenyl)-octanone-3 (11) still gives a pungent compound. On the other hand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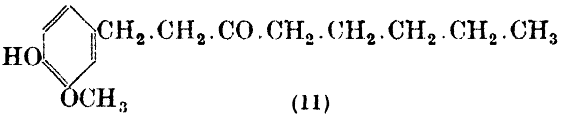
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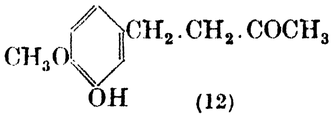
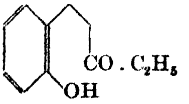

(12)

1-(*m*-hydroxy-phenyl)butanone-3 has only a trace of pungency. *iso*-Zingerone (12)—prepared from *iso*-vanillin has a strongly pungent taste.

Murai[4] has made an investigation of the phenyl ethyl derivatives from which the 4-methoxy group is absent in regard to pungency. He has shown that 1-(*o*-hydroxyphenyl) pentanone-3 (13) is quite pungent and that the molecule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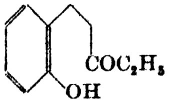
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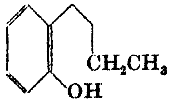
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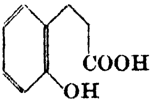
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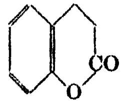
(17)

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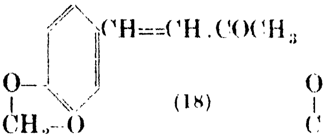
[1] Ichikawa, *Sci. Rep. Tok. Imp. Univ.*, 1925, **14**, 127.
[2] Nomura and Seinosuke, *ibid.*, 1925, **14**, 131.
[3] Murai, *ibid.*, 1925, **14**, 145, 149.
[4] Murai, *ibid.*, 1925, **14**, 145, 149.

retained this property even when the side-chain was altered as in the compounds—

PUNGENT COMPOUNDS

1-(*o*-hydroxyphenyl)-3-phenylpropanone-3 (14).
1-(*o*-hydroxyphenyl) butane (15).
1-(*o*-hydroxyphenyl) propan-acid-3 (16), its anhydride and ester.
Dihydrocoumarin (only faintly pungent) (17).

Nomura and Nozawa [1] prepared samples of the following analogues of zingerone in order to correlate if possible the pungency with some particular group.



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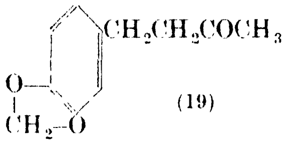

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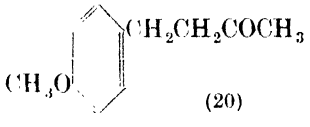

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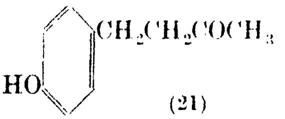

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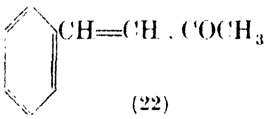

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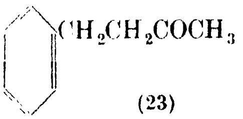

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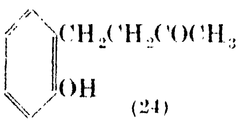

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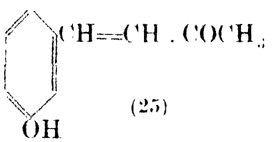

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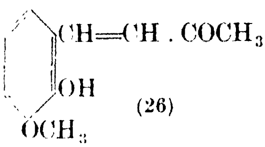

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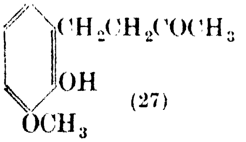

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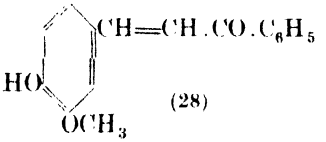

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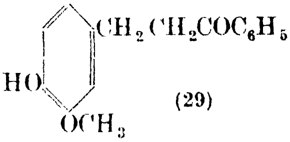


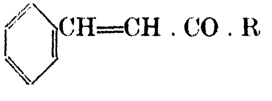
(29)

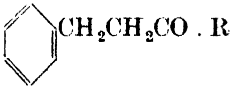
His results may be summarised thus :—

(19), (21), (23) are all pungent.
(24) and (27) are similar in taste, but much less pungent than (19), (21), (23).
(20) and (29) are similar in taste, but much less pungent than (19), (21), (23).
(29) is very similar in taste to zingerone.

(18), (22), (26) and (28) only developed pungency after being on the tongue for some time. The authors conclude that the position of substituents has more effect than the nature of the side-chain.

Pearson [2] examined the pungency of a series of ketones from the two series :—



and


where R is methyl, ethyl or phenyl, with an OH, OCH_3 or methylenedioxy group in the ring. Most pungent of all was 1-(2-hydroxyphenyl)-butene-1-one-3 (30) analogous to the compounds of Murai. Its pungency is still perceptible at a dilution of 1 : 100,000. The compounds (31) and (32)—are still pungent at

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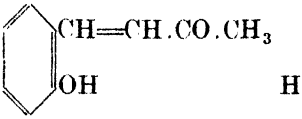
[1] Nomura and Nozawa, *Sci. Rep. Tok. Imp. Univ.*, 1918, **7**, 79.
[2] Pearson, *Pharm. J.*, 1919, **103**, 78.

1 : 30,000. In general, the fully saturated compounds are less pungent than their unsaturated analogues.



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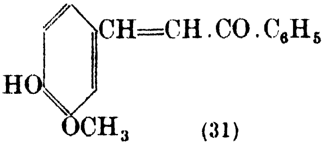
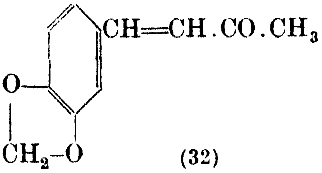
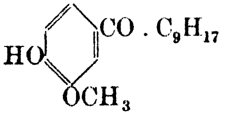


(31)



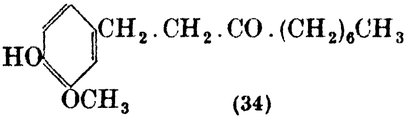
(32)

Shogaol.—Nomura,[1] in 1919, in his extensive researches on the pungent principles of ginger, found that after zingerone had been removed from a ginger extract, there was still remaining a pungent principle which was insoluble in sodium carbonate solution. This he isolated as a yellow oil, $C_{17}H_{24}O_3$, giving it the name shogaol (from " shoga " the Japanese for " ginger "). From his preliminary analyses he ascribed to it the structure (33), the nature of the



(33)

group C_9H_{17} being imperfectly understood. The substance, shogaol, resembles one of the compounds obtained by Garnett and Grier, but was not further investigated until Nomura and Tsurumi [2] in 1927 attacked the problem of the constitution of the side-chain. They observed that the side-chain was unsaturated, and that dihydroshogaol benzoate was identical with the benzoate of 1-(3-methoxy-4-hydroxyphenyl) decanone-3 obtained from gingerol by dehydration and reduction. The dihydro derivative has, therefore the constitution (34).



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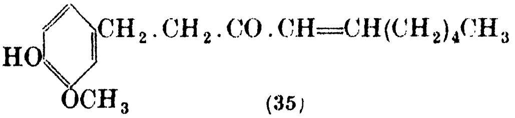
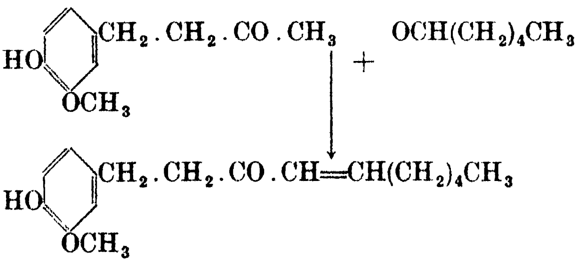


(35)

The position of the double bond is indicated by the refractive index which points to an $\alpha\beta$-unsaturated ketone, from which it is clear that shogaol must be a styryl or an heptenyl derivative ; for various reasons, Nomura preferred the latter conception and formulated shogaol (35).

In a subsequent paper the same authors record the synthesis of shogaol by condensation of zingerone with valeraldehyde :—



Capsaicin.—Capsaicin derives its name from the capsicum, or chili, a species of hot red pepper used widely in tropical countries for flavouring meat and fish dishes. The medicinal capsicum (*Capsicum frutescens*) is used as an external stimulant, and in more than the most minute doses may cause vesication.

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[1] Nomura, *J.C.S.*, **111**, 769.

[2] Nomura and Tsurumi, *Sci. Rep. Tok. Imp. Univ.*, 1927, **16**, 565.

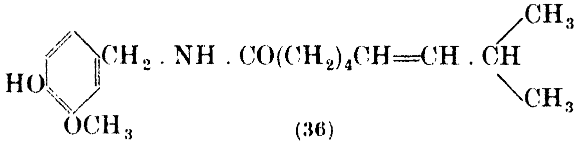
Capsaicin is also found in paprika, of which there are three varieties well recognised in Continental use. These have been described by Zega[1] as :—

1. Those containing capsaicin, employed as a condiment.
2. The long capsaicin-free form.
3. The broad capsaicin-free form.

The two latter are used mainly as a vegetable, and are valuable articles of diet on account of their vitamin content.

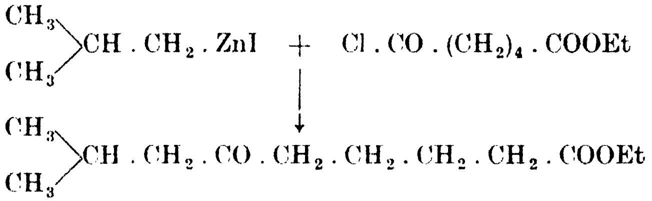
The structure of capsaicin has been worked out comparatively recently ; Lapworth and Royle[2] considered capsaicin to be an oxazole derivative, but this was disproved by Nelson.[3, 4]

Nelson obtained 50 gm. of capsaicin from 50 lb. of very hot cayenne pepper and by oxidation of its methyl compound obtained veratric acid. Hydrolysis of capsaicin gave vanillylamine and a decylenic acid afterwards identified as 8-methylnonene-6-acid-1. The structure of capsaicin was thus proved to be (36)—



(36)

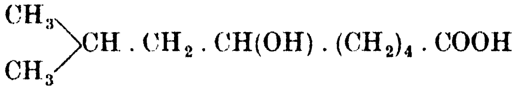
The same author was able to reconstitute capsaicin by allowing the acid chloride obtained from his decylenic acid to react with vanillylamine, when capsaicin resulted. In 1930, Späth and Darling,[5] following on the structural analysis of capsaicin, carried out by Nelson, and independently by Späth and Felmayer, synthesised capsaicin. *iso*-Butyl zinc iodide was treated in cold toluene with the ester of the half chloride of adipic acid, thus producing the ester of 8-methylnonanone-6-acid-1 (37).



$$\left.\begin{matrix}CH_3\\ CH_3\end{matrix}\right\rangle CH.CH_2.ZnI \quad + \quad Cl.CO.(CH_2)_4.COOEt$$
$$\downarrow$$
$$\left.\begin{matrix}CH_3\\ CH_3\end{matrix}\right\rangle CH.CH_2.CO.CH_2.CH_2.CH_2.CH_2.COOEt$$

(37)

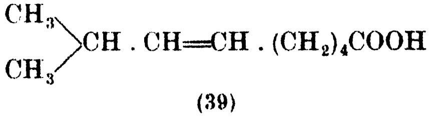
The free acid from this ester may be reduced either by hydrogen and palladised charcoal or by sodium and alcohol to the 6-ol acid (38),



$$\left.\begin{matrix}CH_3\\ CH_3\end{matrix}\right\rangle CH.CH_2.CH(OH).(CH_2)_4.COOH$$

(38)

and by conversion of this acid to its 6-bromo compound, followed by distillation with quinoline, 8-methyl-nonene-6-acid-1 is obtained (39)



$$\left.\begin{matrix}CH_3\\ CH_3\end{matrix}\right\rangle CH.CH{=}CH.(CH_2)_4COOH$$

(39)

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[1] Zega, *Chem. Zgt.*, 1911, **35.**

[2] Lapworth and Royle, *J.C.S.*, 1919, **115**, 1109.

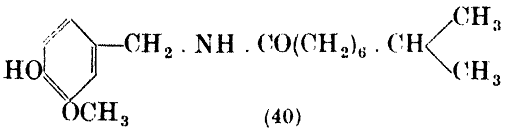
[3] Nelson, *J.A.C.S.*, 1919, **41**, 1115.

[4] Nelson, *ibid.*, 1919, **41**, 2121.

[5] Späth and Darling, *Ber.*, 1930, **63B**, 737.

Condensation of this acid through its chloride with vanillylamine gives capsaicin identical with the natural product.

Further work by Nelson and Dawson[1] showed that the dihydro capsaicin (40)—

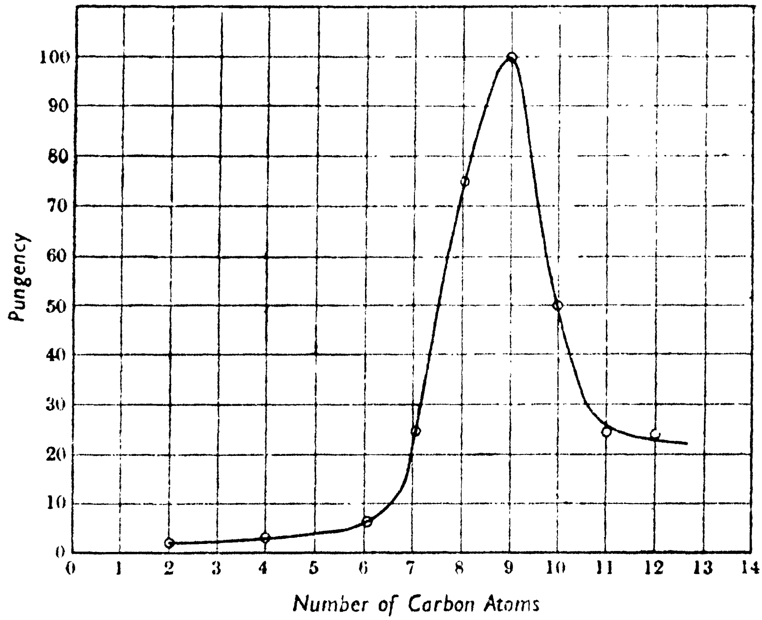


(40)

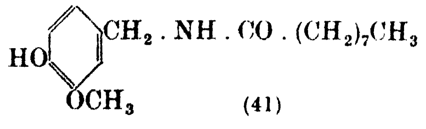
is equally pungent with capsaicin, thus demonstrating that the pungency is not primarily concerned with unsaturation of the side-chain.

Lille and Ramivez[2] have conducted a pharmacological examination of capsaicin, and find the general order of toxicity to be low. Readers are referred for details to the original paper.

Nelson, having established the formula of capsaicin, prepared a series of acylamides of vanillylamine. The pungency of these was measured, and is shown graphically below.



It will be seen that sharp rise is shown after five carbon atoms have entered the chain leading to a strong maximum at C_9-nonoylvanillylamide (41).



(41)

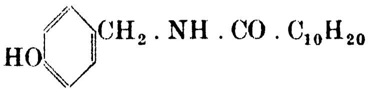
This substance was equal in pungency to capsaicin. On the other hand, Δ^{10}-undecenoylvanillylamide was only one-quarter as pungent as capsaicin, from which it was concluded that pungency is not entirely a function of an unsaturated side-chain.

---

[1] Nelson and Dawson, *J.A.C.S.*, 1923, **45**, 2179.

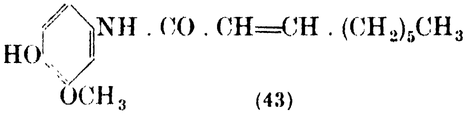
[2] Lille and Ramivez, *Anales. Inst. Biol.* (Mex.), 1935, **6**, 23.

Ott and Zimmermann[1] commenced their investigations with a survey of pungency in the hydroxybenzylamides. Thus undecylenoyl 4-hydroxy-1-benzylamide (42)—



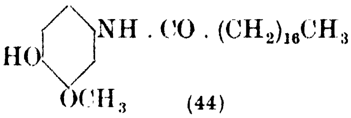
(42)

is pungent, with a sharp note as that of black pepper, although the corresponding 2-hydroxy compound has no pepper taste. Δ^2,-Nonylenoyl vanillylamide (43)—



(43)

possesses a very sharp pepper taste. It was found that whilst stearoyl vanillylamide—



(44)

is devoid of any taste, the corresponding oleic vanillylamide is strongly pungent. Ott and Zimmermann inclined to the opinion that the pungency was to be correlated directly with the unsaturation in the side-chain, but this is at variance with the work of Murai, who showed that the zingerone derivatives still retained their pungency even when the ketonic side-chain was completely reduced to the saturated hydrocarbon radicle.

TABLE X

Vanillylamide of	Pungency (Capsaicin = 100)
n-Nonoic acid	100
α-*iso*-Propyl-*n*-hexoic acid	5
Δ^{ω}-Undecenoic acid	100
Benzoic acid	0·5
Phenylacetic acid	0
β-Phenylpropionic acid	40
γ-Phenyl-*n*-butyric acid	40
γ-Phenyl-*n*-valeric acid	40
β-*p*-Nitrophenyl-propionic acid	20
Cinnamic acid	3
αβ-Dichlor-β-phenylpropionic acid	
Chloracetic acid	
Dichloracetic acid	
Trichloracetic acid	
Bromo and Iodoacetic acids	
Benzylamides	
n-Nono-3, 4-dihydroxy-	25
Δ^{ω}-Undeceno-3, 4-dihydroxy	50
n-Nono-3, 4-methylene dioxy	0
n-Nono-4-hydroxy-	10
Δ^{ω}-Undeceno-4-hydroxy	30
n-Nono-4-methoxy	0

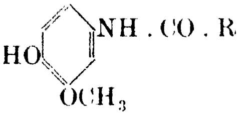
---

[1] Ott and Zimmermann, *Annalen*, 1921, **425**, 314.

A considerable extension of the study of the pungent vanillyl and benzyl amides was carried out by Jones and Pyman.[1] Some of their results are shown in Table X on previous page.

Kobayashi [2] has examined a lengthy series of amides of various acids in a further attempt to correlate chemical constitution and pungency, but without being able to draw many general conclusions. Pungency in the vanillyl amides does not appear to obey any simple rules, and he states that this property does not vary regularly with the number of carbon atoms in the side-chain, although it appears to be related to a free hydroxyl group in the *para*-position.

Speaking generally, it appears that the pungency of the capsaicin series is to be correlated in some way with the acid amide group. Thus Szeki [3] has examined a series of acyl derivatives of amino-guaiacol, and finds certain of them to be possessed of a considerable degree of pungency. The general formula of his compounds is given by

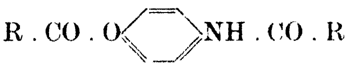


and the main results of his experiments are summarised in Table XI.

TABLE XI

Group R . CO in above formula	M.P.	Degree of pungency
iso-Butyryl	142°	+
n-Heptylyl	110°	+ + +
Δ^2-Nonenylyl	93°	+ + +
Capryl	100°	+ + +
Δ^{10}-Undecylenyl	89°	+ + +

In addition, he examined a series of compounds derived from the general formula



by varying the group R. They were obtained by the action of the acid chloride on *p*-aminophenol. The degree of pungency and composition of these compounds is indicated in Table XII :—

TABLE XII

Acid from which compound is derived	M.P.	Pungency
Δ^{10}-Undecylenic	111°	+ +
Nonylic	121°	+ +
Δ^2-Nonylenic	84°	+
Heptylic	119°	+

Note.—Pungency is expressed in the three degrees.

+ + + 3 mg. 150 cc., pungent taste.
+ + 3 mg. 1 c.c., pungent taste.
+ Barely perceptible taste.

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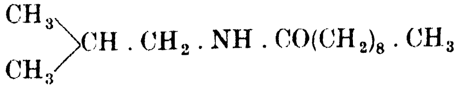
[1] Jones and Pyman, *J.C.S.*, 1925, **127**, 2588.

[2] Kobayashi, *Sci. Papers Inst. P.C. Res.* (Tokio), 1927, **6**, 166.

[3] Szeki, *Arch. Pharm.*, 1930, **268**, 151.

Finally, it is interesting to note that Asahina and Asano[1] had traced the high pungency of Para-cress to the presence of spilanthol, which they stated to be related to *n*-decoyl*iso*butylamide, in which certain features of the capsaicin



$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>CH\,.\,CH_2\,.\,NH\,.\,CO(CH_2)_8\,.\,CH_3$$

molecule are discernible; later work, however, showed that spilanthol, the substance in question, contained two atoms of hydrogen less than was originally thought, and degradative oxidation with ozone showed it to be the *iso*-butylamide of a nonenecarboxylic acid, possibly

$$(CH_3)_2CHCH_2NHCOCH_2CH_2CH = CH(CH_2)_4CH_3$$

Similarly, Gulland and Hopton have shown that pellitorine is a closely related pungent principle.

ODOUR

The sense of smell, as far as the human race is concerned, has become less acute through the ages that have elapsed between the existence of primitive man and the present time. It is commonly held that animals possess a sense of smell that is far more acute than ours, just as many of the inhabitants of the bush are accredited with a keener sense of sight and hearing than domestic creatures. It would seem, then, that those faculties are most keenly developed that constitute the greatest advantage in the environment in which an animal exists; from which it may justly be observed that as civilisation has developed, and man has been forced less and less to depend on his own activities in the field for safety, food and so forth, the faculties of the senses, more especially that of smell, have become less active. Primitive land animals lived in a world where perception must have been mostly dominated by the smell of things. In their evolutionary progress, vision and hearing have become relatively more important, and in the higher animals all three are well represented. In man the power to perceive and differentiate between various smells has diminished, but this decline is not always apparent, since partial loss of the ability to smell (*anosmia*, if complete) does not give us such immediate inconvenience, or even discomfort, as the loss of any of the other faculties; with individuals whose nose and palate show comparative insensibility (and there are many such) the loss would pass almost unnoticed.

In considering the scientific basis of odour, the matter may be divided into two sections :—

1. The physiological basis of odour-perception.
2. The physical basis of the osmic stimulus.

That part of the nose associated with the perception of smell consists of a layer of cells, long and narrow, which are arranged with their length perpendicular to the plane of the nasal cavity. These cells are of two kinds, the sustentacular cells, the outer end of which is broad and blunt, and which serve to support the more delicate olfactory cells associated with the actual process of perception. The olfactory cells are elongated, the inner being connected to the nervous system, the outer end being freely exposed to the air in the nostrils. This free end terminates in a small clear projection which passes through the cuticular membrane and is furnished with a number of stiff, hair-like projections. These are kept moist by the mucous secretion of the nose, without which perception would be almost impossible. It may be added that the olfactory hairlets just described are less prominent in man than in other animals, and appear to be most strongly developed in the amphibia, birds and reptiles. The stimulus received by these terminal fibres is passed by the body of the cell to the nerve fibre and thence to the brain. The surface of the nose, therefore, presents to the free space of the nostrils a series of minute hair-like projections, moistened with mucous, which acts as the osmic sensory processes. It is obvious that during the incidence of colds, when the mucous linings are inflamed and covered with thickened mucous, or in catarrh when a similar condition exists, the ability to smell will be considerably diminished and in some cases completely inhibited by reason of the osmic sensory processes being cut off from access to the air.

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[1] Asahina and Asano, *J. Pharm. Soc. Japan*, 1922, 85.

There has been much controversy over the nature of odour perception, some of which still continues. Nevertheless, some facts are quite clear. In the first place, the sense of smell is not necessarily connected with any of the other perceptive faculties although, like them, it is perceived by specialised nerve endings in a specialised epithelium. There was at one time a suggestion made that the sense of sight and taste were interconnected, and that the sense of smell was less acute in the dark than in the light, but there is no experimental evidence to support this; indeed, Dugald Stewart records the case of a boy who was born blind, deaf and dumb, but showed abnormally active smelling faculties.

The problems of odour perception are two; the question as to what passes between the odorous body and the nose in order to produce the sensation and, secondly, the nature of the mechanism by which the sensation is created and received within the nose itself. During the last century a definite answer has been given to the former question, namely that for a substance to stimulate the sensory processes of the nose it is necessary for some of its molecules to leave the main portion of the substances and pass into the nasal cavity and onto the smell-sensitive cells contained therein. That this was by no means, until recently, the common view is indicated in the 6th edition of T. Reid's "On Smelling", in which it is suggested that odorous substances "are continually sending forth effluvia of vast subtility", while in "An Inquiry into the Human Mind on the Principles of Common-sense" he discusses the problem as to "whether as some chemists conceive every species of bodies hath a spiritus rectus, a kind of soul, which causes the smell". There is contained in these suggestions the germ of the idea that smell may be due to an emanation from the odorous compound, although the author does not indicate its precise nature; we are, indeed, to suppose that he did not support the theory that odour is due to the perception of vibrations, since he says, later, "we have no variety of vibrations corresponding to the immense variety of sensations which we have by sight, smell, taste and touch". The idea of a spiritus rectus (more exactly "spiritus rector") is derived from Boerhaave (1668–1738), a Dutch physician, who postulated that every odorous substance has two parts, the "resinous substance" or matter and the very subtle, nearly unweighable, "ether", which was the spiritus rector. It was soluble in water, whilst the resinous part was not.

The two hypotheses which stood side by side were these, that on the one hand, odour sensations might be due to the perception of vibrations transmitted in some way from the substance to the sensory apparatus, or due, on the other hand, to the actual particles of the odorous substance impinging onto the sensitive cells of the nose. The former hypothesis arose from an analogy; our sensations of light and heat are due to the stimulation of the appropriate apparatus of the body, by vibrations in the ether and our auditory apparatus is stimulated by vibrations in the air, what could be more natural than to suppose that our olfactory sensations should be stimulated by vibrations from the odorous substance? This hypothesis is correct enough, but its early exponents went too far in asserting that the vibrations could pass through the space separating the odorous body from the nasal receptive apparatus. It has been established that actual contact between the molecules of the odorous substance and the osmic cells is necessary before the perception of smell can take place. This being so, it is obvious that some mechanism must exist by which the molecules can reach the nose; this mechanism is comprised in the phenomena of vapour pressure, or the tendency of certain substances to evaporate.

Certain substances have, even at ordinary temperatures, a tendency to evaporate, whilst others are comparatively permanent; the former part with their component molecules which pass off into the air, whilst the molecules of the latter have no tendency to pass off in this way. Camphor and turpentine are good examples of the former class, iron and glass of the latter; the former, tending to evaporate, show a vapour pressure, and the latter have either no vapour pressure or one which is insignificantly small. To be odorous, a substance must have a perceptible vapour pressure. It is, therefore, the invisible wandering particles of a substance which come to rest inside the nose, and having, so to speak, anchored themselves in the haven of the olfactory cells, proceed to stimulate the latter in their own peculiar way. The amount of material required before a sensation is registered at the olfactory cells is almost unweighable; Newton exposed a grain or two of musk to the air of his study and observed that, after several years, it had not altered appreciably in weight, although it had perfumed the room throughout the whole of this period. Later experiments have shown that there is a very small loss of weight when such substances are exposed for prolonged periods. From the standpoint of weight, therefore, the nose can perceive an incredibly small amount of matter. Strong smelling substances such as ionone can be perceived in one normal inspiration containing only 0·00000000001 of a gram, a quantity so small that it cannot be weighed directly, but must, like astronomical distances, be computed. On the other hand so small is the molecule of these substances, that the small quantity just mentioned will contain 1,600,000 molecules. This quantity appears to be the minimum that will cause the sensation of odour.

The second problem of odour, referred to above, is that of the mechanism by which the odorous particles, once in contact with the sensory processes, give rise to their characteristic odour sensation. Chemical theories have been advanced from which there is more divergence than adherence, and the subject merits careful consideration. It appears that the first essential, after volatility, for an odorous substance is solubility in lipoid (fatty) matter. All odorous substances are soluble in lipoid matter, and it appears that the hair-like terminal of the olfactory cell is sheathed with lipoid matter. It has been suggested that the mere solution of the odorous substance in the lipoid of the terminal sheath disturbs a chemical equilibrium, and so sends an impulse to the brain. This hypothesis fails to account for the vast variety of odour sensations; a chemical equilibrium cannot be upset in a variety of ways, only to varying degrees, and, moreover, it is difficult to see why a strong smelling substance in small quantities should not produce the same degree of disturbance as a higher concentration of less active substance. Another hypothesis is that oxidation of odorous substances gives rise to vibrations which are perceived by the nose; but this cannot bear a rigid examination. Substances such as hexane and diphenyl oxide have a powerful smell, but cannot be oxidised readily even with the powerful reagents of the laboratory; it is apparent that any hypothesis which seeks to explain the odour of these substances must bear this fact in mind. There is an additional fact which assists in the disposal of the oxidation theory of odour perception, namely, that odorous substances still exert their characteristic smell in atmospheres of hydrogen and nitrogen, where oxidation is impossible.

There is a general tendency to refer to the problem of "the relation of odour to chemical constitution" as though a direct correlation existed between odour and the gross details of chemical structure. This is not so, and much confusion has been caused by this conception, which has arisen from a false analogy with the so-called "problem" of colour and constitution. This matter is part of the general problem of the inter-relation between physiological action and chemical structure, and may best be considered as follows. In the first place, the ability of an organic compound to produce a physiological effect presupposes a physical conjugation between the substance under consideration and some sensitive organ or process in the animal system. In drug action, the drug must be brought physically into contact with the processes on which it is to act; in colour perception light modified by transmission through or reflection from the coloured body must impinge upon the eye; with sound, the aerial vibration must enter the ear. In the second place, the physiological activity must be caused by some property peculiar to the substance examined, reacting upon the sensory processes. The reaction may be chemical, as in the case of certain sulphonamides which interfere with metabolism of bacteria, competing for their nutritional essentials in such a way as to starve them; it may be physico-chemical, as in the perception of light where the stimulus of light produces its effect by bleaching the visual purple converting it to the orange pigment retinene.

There is little doubt that the correct mechanical picture of odour stimulus is achieved by consideration of :—

(*a*) A direct contact of molecules of odorous substances with the sense organ.

(*b*) The perception of some physical property of the molecules, peculiar to themselves.

This latter property is comprised in the periodic rotational or vibrational movements of the individual parts of the molecule. The implications of such an hypothesis are as follows :—

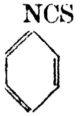
1. Since the molecules of all substances are able to show these intramolecular frequencies, it follows that all substances must have the potentiality of odour. To account for the absence of odour in many such compounds it is necessary to assume that only such vibrations can be perceived as fall within a certain range—the "range of osmic sensation". The parallel with colour perception is important here—practically no substance is without some absorptive capacity for electromagnetic vibrations from the infra-red to the ultraviolet; this is a fundamental attribute of matter; whether this absorption falls within the comparatively narrow limits of visual frequency, however, depends on a large variety of circumstances. When the so-called "correlation of colour and constitution" theory was in its ascendancy, it was customary to attempt to trace the factors causing absorption to fall within visual limits, to certain groups, or combinations of groups, the "chromophores" and "auxochromes". It cannot be said that such attempts were uniformly successful, and the most that can be said is that certain configurations, mainly unsaturated groupings, cause such disturbances in the molecule as predispose towards absorption in the visible spectrum. (See also Vol. III, Chap. VII.)

So with odours: certain chemical groups and configurations (mainly, but not exclusively, those of unsaturation) lead to the development of intramolecular frequencies capable of affecting the osmic sensory processes. These are referred to, subsequently as the "osmic frequencies".

2. The connexion between chemical constitution and odour is therefore an indirect one; entirely dissimilar structures may, through the accidents of quantum mechanics engender similar osmic frequencies; and configurations which appear chemically similar may have different osmic frequencies.

When we find such chemically diverse substances as hydrocyanic acid, benzaldehyde and nitrobenzene with odours which, in appropriate concentration, are similar in many ways, it clearly becomes necessary to search for some property which they all possess in common, and which may be correlated with their effect on the osmic sensory processes. A similar example is to be found in the odours of the highly chlorinated hydrocarbons such as hexachloroethane and benzene hexachloride which both resemble camphor, as also does tetrachloronaphthalene; whilst the curious similarity between the odours of iodoform and *s*-trichlorophenol will be familiar to all who have handled these compounds. Numerous other instances will occur to those familiar with the odours of organic compounds.

As examples of the opposite type, reference may be made to the investigations carried out by Dyson[1] on the odours of aryl and aralkyl thiocarbimides. Thus, phenylthiocarbimide (45) has a characteristic, pungent odour which is similar in many ways to that of *m*-tolyl thiocarbimide (46); on the other hand, *p*-tolyl thiocarbimide (47) has the sweet and penetrating odour of aniseed.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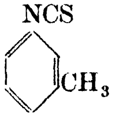
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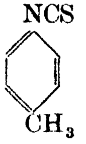
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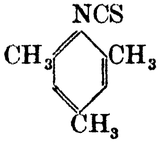
(48)

Further alkyl substitution, as in mesityl thiocarbimide (48) intensifies the pleasant characteristic of the odour, leading to a floral spiræa-like perfume: Many similar instances were observed where the substituents were halogen, cyano- or methoxyl groups. In these examples, it is abundantly clear that these large osmic differences cannot be attributed to changes in chemical constitution, but must be due to physical differences engendered by the orientation of the constituent groups.

A molecule of an odorous substance, such, for example, as benzaldehyde, may be taken as that of an assemblage of atoms arranged in the accepted configuration of the organic chemistry, but nuclei and electrons of the atoms are not static; they move about a mean position and are dynamic in the sense that they have a periodic motion with regard to their fellows. Not all such motions are perceptible by the osmic sensory system, but certain of them which are so perceptible constitute the *osmic frequencies* of the molecule, and it is these which are able to affect the sensitive membranes of the nose and so give rise to the sensation of smell.

It has often been lamented that there has been no method by which the nature of an odour can be measured, and that whilst both colour and sound were amenable to a detailed vibrational analysis, odour could only be somewhat unsatisfactorily discussed in terms of analogy and vague attempted description of the personal effects produced. If the fundamental principle of the concept of odour as the perception of intramolecular osmic frequencies be adopted, then the approach to the basic scientific analysis and measurement of odour lies in the measurement of these intramolecular frequencies. To amplify this statement, if the physicist wishes to obtain an exact measurement of the vibrations associated with a certain organ pipe he uses an instrument which will register both the frequency and intensity of the various vibrations set up when the column of air in the pipe is thrown into a state of motion by the act of "blowing"; he makes, as it were, a map of all the vibrations set up in his sound system; he knows, of course, that some of them are too rapid, and others too slow, to be heard by the human ear, but the *audible frequencies* are those responsible for the note we hear from this particular organ-pipe; the physicist knows also that no matter how such vibrations are produced, so long as they are exactly the same in frequency and intensity, they will produce the same effect on the human ear; it is only recently that an electric organ without any pipes at all has been constructed, which is able to produce all the sensations of organ tone by electrical apparatus depending on the production of vibrations identical with those from the pipes of any ordinary organ. We must, therefore, in our consideration of the physics of odour, search for some means of measurement of the vibrations set up inside the molecule.

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[1] Dyson, *Perf. and Ess. Oil Record*, 1928, 8, 88, 171; 1929, 2 and 42.

The suggestion has been made by Dyson [1] that there may be a correlation between the osmic frequencies and the Raman shifts, since the latter reveal something of the intramolecular vibrations.

THE PERFUMERY INDUSTRY

The production of perfumes for æsthetic enjoyment and of flavours for the improvement of foodstuffs occupies a considerable industry. One large section is employed in extracting the odorous oils from plants, flowers and fruit in order to condense into a small compass the odorous materials. The main methods employed in the extraction of these volatile materials are :—

(1) *Distillation*, with steam. Thus, the bales of harvested peppermint plant, the chopped camphor- or sandal-woods or the roses are placed in large stills with water and subjected to the action of steam which carries off the volatile materials, these being separable from the condensate. Yields are quite small; Mitcham peppermint yields about 16–22 lbs. of oil per acre of plantation; a pound of Bulgarian rose-otto requires over a thousand acres of roses.

(2) *Expression*, as with the lemon, orange and bergamot oils obtained by simple rasping and pressure of the peels.

(3) *Extraction with volatile solvents* is sometimes practised but more often the extraction is carried out with a low melting, deodorised animal fat which extracts the volatile flower oils and gives a pomade of high value. The odorous constituents can readily be transferred to alcohol by extracting with the warm spirit, in which the fats are only slightly soluble.

(4) *Enfleurage* is a process by which the flowers are placed in contact with a layer of lard which has been solidified on a glass tray. The trays are placed in cool, dark cupboards and the essential oils distil slowly into the lard. Good yields are obtained, since the flowers live and produce perfume for some days, instead of being immediately killed by the solvent or temperature of more drastic methods. Fresh petals are placed on the lard at intervals, and the perfume may then be transferred to alcohol as in the fat extraction method. The method is particularly successful with jasmine and rose.

The production of the concentrates by the above methods yields the main raw material of the flavouring and perfume industry, and the individual terpene constituents of these mixtures have been discussed chemically in the main body of this chapter. It is, however, very seldom that the raw concentrates can be used directly, even when suitably diluted, for perfuming and flavouring. Thus, during their preparation certain small traces of labile constituents may have been lost; these will have to be replaced; others may have been modified and their modified odour may need correcting; fixatives may be necessary to improve the persistence of the odour in use. The art of building perfumes or flavours is to improve the natural essence or extract by the addition of other natural or synthetic isolates. Tolerably good imitations of natural perfumes can be obtained wholly from combinations of synthetic materials, and for some purposes, e.g., soap-perfuming, are to be preferred to natural concentrates.

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[1] Dyson, *Perf. and Ess. Oil Record*, 1937, **28**, 13.

Among the more widely used materials of perfumery (excluding the terpenes and floral isolates) are :—

1. *Higher Aliphatic Aldehydes.*

Capryl aldehyde $C_7H_{15}CHO$.
3-Methyl nonyl aldehyde (3-methylnonanal),
$CH_3(CH_2)_5\,CH(CH_3)CH_2\,CHO$
3-Methyldodecyl aldehyde (3-methyldodecanal),
$CH_3(CH_2)_8CH(CH_3)CH_2CHO$
Undecyl aldehyde ('C_{11}-aldehyde '),
Lauraldehyde (dodecanal or 'C_{12}-aldehyde ').

The three latter are used in small quantities in nearly all floral perfumes, and are actually found in natural perfumes, whilst unsaturated nonadienal-2, 6 ($CH_3CH_2CH{=}CH\,.\,CH_2CH_2CH{=}CHCHO$) has been isolated from violet-leaves. In the aromatic division the use of vanillin, coumarin, piperonal, etc., in flavouring is well established.

2. *Ketones.*

Reference has already been made (Chap. VI, Appendix II) to the ring ketones of interest in the perfumery industry. Some of the higher normal ketones have powerful odours, and can be used in certain perfumes and flavours. The following are notable :—

Methyl heptyl ketone (nonanone-2), $CH_3CO(CH_2)_6CH_3$,
Methyl octyl ketone (decanone-2), $CH_3CO(CH_2)_7CH_3$,
Methyl nonyl ketone (undecanone-2), $CH_3CO(CH_2)_8CH_3$

all from *Ruta graveolens.*

The first of the above group with methyl amyl ketone (heptanone-2), $CH_3COC_5H_{11}$, are found in Roquefort cheese.

3. *Esters.*

The odour of ' pear-drops ' is one of the earliest experiences of the organic chemist, and the use of '*iso*amyl acetate ' for flavouring these sweets is one of the earliest uses of a ' synthetic ' flavouring. The use of this material is an example of what is often termed a ' conventional ' flavour ; to be successful, pear-drops must taste of *iso*amyl acetate—not of pears. Another instance is use of allyl caproate which gives the excellent, but ' conventional ' pineapple flavour of the trade. Some of the more interesting flavour esters are described in Table XIII.

In addition, a large number of higher esters of powerful odour such as octyl acetate, octyl butyrate and octyl caproate (all of which are found in parsley) have been only slightly investigated from a flavouring standpoint.

4. *Ethers.*

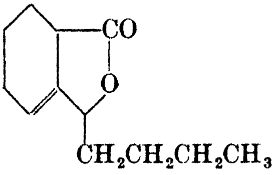
One or two ethers—anethole and diphenyl ethers—are used in perfumery on account of their pleasant odours.

In addition to the four classes mentioned above, there are one or two individual substances which are of interest. Thus, sedanolide, the odoriferous constituent of celery, is a lactone (49) ; other odorous lactones, e.g., those from ambrette and angelica have been mentioned previously (p. 444). Jasmone, an important constituent of jasmine perfume is a cyclic ketone (1-methyl-2, (2-pentenyl)*cyclo*pentenone-3) (50). Equally interesting is the so-called ' methyl

TABLE XIII

Alcohol	Acid	B.P.	Characteristics	Uses in essences
Ethyl	formic	55°	Strong flavour of rum	Raspberry, red currant, peach
Ethyl	acetic	77°	Strong, but indefinite fruit odour	Apple, pear, and all soft fruit essences
Ethyl	butyric	120°	—	Pineapple, banana, strawberry
Ethyl	*iso*-valeric	134°	Has a definite raspberry note	Raspberry, peach
Ethyl	heptoic	187°	Ditto	Raspberry, red currant
Ethyl	pelargonic	227°	Strong quince flavour	Quince
Allyl	caproic	242°	Pineapple	Pineapple
iso-Amyl	acetic	142°	—	Pear-drops
iso-Amyl	butyric	178°	—	Soft fruit essences
iso-Amyl	*iso*-valeric	194°	Found in essential oil of bananas	Apple, pineapple, peach

heptine carbonate'—the methyl ester of octyne-2-acid-1 (52). It may be prepared from the œnanthal (51) obtained by the destructive distillation of castor-oil, by the steps shown in the scheme below. The ester has a fresh violet odour. Yet another group of compounds of interest are the sulphur compounds responsible for coffee aroma; this aroma, it may be added, is only produced during roasting and comprises a wide range of volatile products.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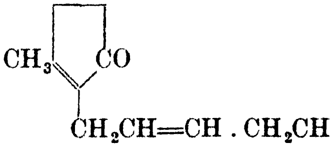
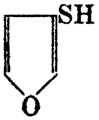

(50)

$$\begin{tikzcd}
\underset{(51)}{CH_3(CH_2)_5CHO} \arrow[r, "PCl_5"] & CH_3(CH_2)_5CHCl_2 \arrow[r, "2KOH"] & CH_3(CH_2)_4C{\equiv}CH \arrow[d, "CO_2"] \\
 & \underset{(52)}{CH_3(CH_2)_4C{\equiv}C\,.\,COOMe} & CH_3(CH_2)_4C{\equiv}C\,.\,COOH \arrow[l]
\end{tikzcd}$$

These include diacetyl, $CH_3COCOCH_3$, acetylpropionyl, $CH_3COCOCH_2CH_3$ (to which, incidentally, butter owes its flavour), ketones of the furan series, particularly furyl methyl ketone (55), together with furyl and thienyl thiols (53) and (54). There is no doubt that other and more complex sulphur compounds are present, together with derivatives of pyridine and the alkyl-pyrazines.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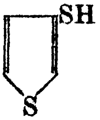
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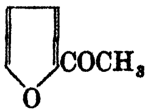
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CHAPTER X

POLYALCOHOLS, CARBOHYDRATES AND RELATED COMPOUNDS

> " Some are termed sugars (*σάκχαρον*), being a solid honey found in canes (*ἐπὶ τῶν κάλαμων*) coming from India and Arabia Felix, in consistence like salt, and capable like salt of being ground to powder between the teeth."
>
> —DIOSCORIDES, " On different kinds of honey ".

Sweet substances have attracted man's attention as articles of food from the earliest times, and sugar as such was known in the East at least two thousand years ago, the use of crystalline sugar being introduced into Europe during the time of Alexander the Great. In this country and in Northern Europe its use was strictly limited by its high cost, and honey was more common, being indigenous. It is interesting to note that Libavius in his ' Alchymia ' of 1595 refers to ' Sacchari crystallini quod candi appelant '. During the seventeenth century the working of sugar cane was brought to a commercial stage and in the early part of the eighteenth century cane sugar was an article of commerce. In 1747 Margraaf pointed out the existence of considerable quantities of sugar in beet and other fleshy roots, and impressed on the continental authorities the potentialities of the beet as an independent source of sugar ; it took a century and a half for the idea to become an industrial achievement in this country.

Quite naturally other products were shown to contain saccharine substances allied to cane sugar ; in 1619 Fabrizio Bartoletti drew attention to the ' sugar of milk ' which was thoroughly examined by Ludovico Testi in 1698, and pronounced by him a valuable medicine. Glauber was acquainted with the distinct nature of glucose in 1660. The early part of the nineteenth century showed concentrated efforts directed towards the isolation of new sugars from natural sources ; in 1802 Proust showed the identity of the sugar from honey and grape sugar with that obtained from other sources, and Dumas christened it ' glucose '. Later, in 1806, mannite was isolated by Proust from manna, and although not a true sugar, was so much like one in many respects as to be classified temporarily with the group. Erdmann and Pasteur found that milk sugar was hydrolysed by dilute acids to give a hitherto unrecognised sugar which they wished to call ' lactose ' but Berthelot successfully pleaded for a new name ' galactose ', leaving ' lactose ' itself as the proper name for the original sugar of milk. Meanwhile Kirchoff (1811) had isolated maltose from the products of the acid treatment of starch, and for years chemists speculated about its true nature until O'Sullivan[1] cleared up its individuality. In 1836 Hünefeld isolated dulcite, and Stenhouse erythrite, whilst glycogen or ' animal starch ' was isolated by Claude Bernard from liver in 1857, Valentine Rose having many years previously (1811) recognised inulin from the root of elecampane as a distinct form of starch.

It will already have been noticed that certain substances have been mentioned which are not, strictly, carbohydrates. The original meaning of the word was " a substance containing carbon, hydrogen and oxygen, the two latter elements being present in the correct proportions to constitute water ". The field is broader than is implied by this definition, methyl pentoses, for example, not coming within its strict import ; they will, however, for the purposes of this book, be included with the carbohydrates—as also will be the polyhydroxylic alcohols from erythrite onward. The consideration of this extremely large family will be subdivided in the following way :—

---

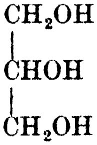
[1] O'Sullivan, *J.C.S.*, 1872, 579 ; 1876, [i] 478.

(1) The structure of the monosaccharides.
(2) The individual monosaccharides.
(3) The structure of disaccharides.
(4) The individual disaccharides.
(5) The higher sugars.
(6) The general synthetic and degradative reactions of sugar chemistry.
(7) The polysaccharides.

The division of the sugar family into mono-, di-, tri- and higher saccharides is dictated by the number of individual sugar units which their structure comprises ; each unit may be an *aldose* or *ketose*, according as the substance carries an aldehyde or keto- group.

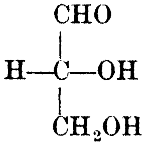
THE STRUCTURE OF THE TRIOSES

Trioses, or three-carbon sugars, are not numerous, owing to the simplicity of the carbon chain. The alcohol of the series, glycerol (1), has already been discussed in Chapter V (p. 296).



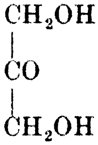
$$\begin{array}{c} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

(1)



$$\begin{array}{c} CHO \\ | \\ H—C—OH \\ | \\ CH_2OH \end{array}$$

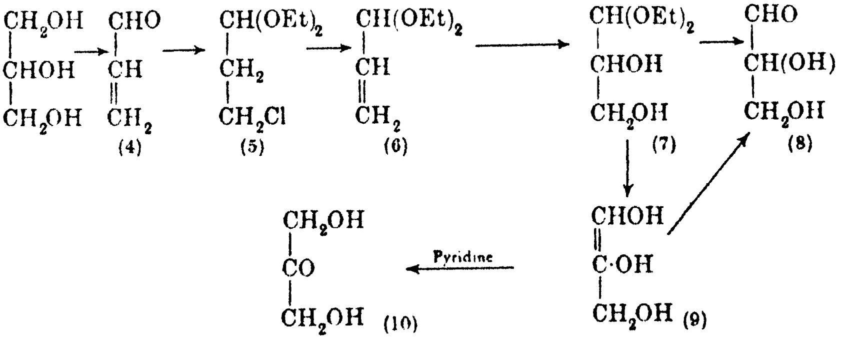
(2)



$$\begin{array}{c} CH_2OH \\ | \\ CO \\ | \\ CH_2OH \end{array}$$

(3)

The two possible trioses are (*a*) the aldo-triose, glyceric aldehyde (propanaldiol-2, 3) (2) ; and (*b*) dihydroxyacetone or propanonediol-1, 3 (3). The synthesis of glyceric aldehyde is difficult ; it is almost impossible to obtain a satisfactory yield by the direct oxidation of glycerol, and a roundabout method must be used ; this is illustrated by the formulæ below.



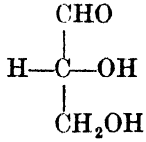
If acrolein (propen-2-al) (4) from glycerol is treated with alcoholic hydrogen chloride the acetal, 1, 1-diethoxy-3-chloropropane (5) is formed which may be converted to the acetal of acrolein (6). This can be oxidised to the acetal of glyceric aldehyde (7), from which the free aldehyde (8) can be obtained by acid hydrolysis. The final stage is not a simple one, since during the splitting of the acetal the first product is a definite enol form [1] (9) which, as a thick viscous syrup, can either be allowed to turn spontaneously into glyceric aldehyde or may be converted by boiling in pyridine solution to dihydroxyacetone (10) [2].

---

[1] **Reeves, *J.C.S.*, 1927, 2478.**

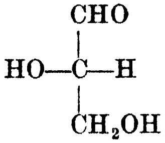
[2] **Fischer *et al.*, *Ber.*, 1927, 60, 479.**

It will have been noticed from formula (8) that glyceric aldehyde has an asymmetric carbon atom, and that it can therefore exist in dextro- or lævo-forms. These, indeed, have been prepared through the *l*-menthyl urea derivatives, and may be written thus :—



$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-glyceraldehyde



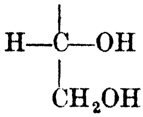
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CH_2OH}\end{array}$$

L-glyceraldehyde

This is the first application of a convention which must be mastered at the outset of sugar chemistry, the rules of which are as follows :—

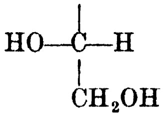
(1) All sugars are written with the formulæ vertical, —CHO at the top, —CH_2OH at the bottom. In the case of ketoses the carbonyl group is placed so as to be as near the top as possible.

(2) Any sugar whose lowest groups are



$$\begin{array}{c}|\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

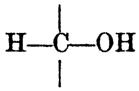
is described as a D-sugar *irrespective* of whether it is *dextro-* or *lævo*-rotatory ; and the converse is also accepted, namely, that any sugar with the lowest groups written thus :—



$$\begin{array}{c}|\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CH_2OH}\end{array}$$

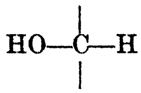
is described as a L-sugar.

(3) The group



$$\begin{array}{c}|\\ \mathrm{H{-}C{-}OH}\\ |\end{array}$$

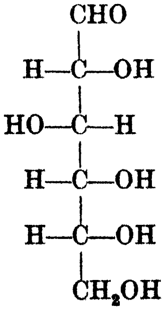
is often written by the plus sign alone (+), and the group



$$\begin{array}{c}|\\ \mathrm{HO{-}C{-}H}\\ |\end{array}$$

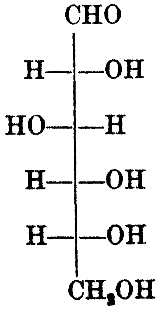
by the minus sign (−).

Thus the sugar D-glucose (which is so-called because of the accepted



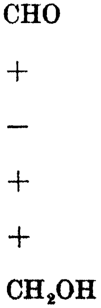
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

(11)



$$\begin{array}{r|l}\multicolumn{2}{c}{\mathrm{CHO}}\\ \mathrm{H-} & \mathrm{-OH}\\ \mathrm{HO-} & \mathrm{-H}\\ \mathrm{H-} & \mathrm{-OH}\\ \mathrm{H-} & \mathrm{-OH}\\ \multicolumn{2}{c}{\mathrm{CH_2OH}}\end{array}$$

(12)



$$\begin{array}{c}\mathrm{CHO}\\ +\\ -\\ +\\ +\\ \mathrm{CH_2OH}\end{array}$$

(13)

$$\begin{array}{c}+\\ -\\ +\\ +\end{array}$$

(14)

configuration of the lowest active carbon atom) happens to be *dextro*-rotatory- (some D-sugars, e.g., D-arabinose, are *lævo*-rotatory) and is written (11) or (12), but by substituting the + and − convention can become (13) or even (14).

(4) In dealing with the problems of stem configuration in simple sugars no account is taken of the fact that pentoses and hexoses often form inner ethers, a matter which can be considered in detail later.

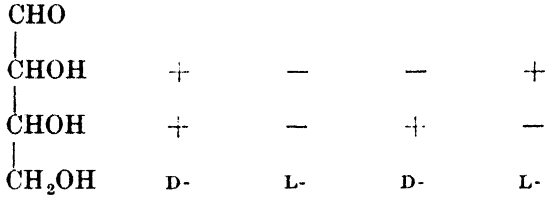
(5) It should be realised also, that the optically active sugars exist in pairs D and L; the L form is the complete reversal of the plus and minus structure of the core. Thus,

$$\text{if D-glucose is } \begin{array}{c} + \\ - \\ + \\ + \end{array} \quad \text{L-glucose will be } \begin{array}{c} - \\ + \\ - \\ - \end{array}.$$

It follows, therefore, that the number of sugars of the aldose series will be expressed by 2^n, where 'n' is the number of asymmetric carbon atoms; thus there are $2^4 = 16$ hexoses, or eight pairs of D and L enantiomorphs.

THE ALDOTETROSES

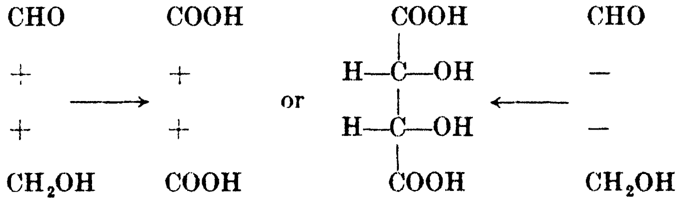
The simple aldotetrose structure (15) contains only two asymmetric carbon atoms and the four possible structures are :—



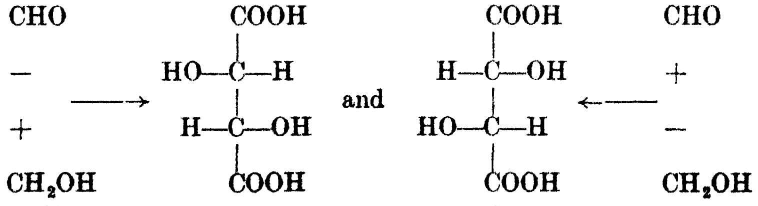
$$\begin{array}{lcccc} \text{CHO} & & & & \\ | & & & & \\ \text{CHOH} & + & - & - & + \\ | & & & & \\ \text{CHOH} & + & - & + & - \\ | & & & & \\ \text{CH}_2\text{OH} & \text{D-} & \text{L-} & \text{D-} & \text{L-} \end{array}$$

(15) erythrose threose

There are therefore two pairs of sugars, D- and L- erythrose, and D- and L-threose. The assignment of the structures to these is based on the following grounds. Erythroses give the same mesotartaric acid on oxidation; threoses give an active tartaric acid. This may be expressed thus :—



$$\begin{array}{c} \text{CHO} \\ + \\ + \\ \text{CH}_2\text{OH} \\ (16) \end{array} \longrightarrow \begin{array}{c} \text{COOH} \\ + \\ + \\ \text{COOH} \\ \end{array} \quad \text{or} \quad \begin{array}{c} \text{COOH} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—C—OH} \\ | \\ \text{COOH} \\ A \end{array} \longleftarrow \begin{array}{c} \text{CHO} \\ - \\ - \\ \text{CH}_2\text{OH} \\ (17) \end{array}$$

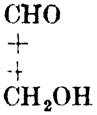


$$\begin{array}{c} \text{CHO} \\ - \\ + \\ \text{CH}_2\text{OH} \\ (18) \end{array} \longrightarrow \begin{array}{c} \text{COOH} \\ | \\ \text{HO—C—H} \\ | \\ \text{H—C—OH} \\ | \\ \text{COOH} \\ B \end{array} \quad \text{and} \quad \begin{array}{c} \text{COOH} \\ | \\ \text{H—C—OH} \\ | \\ \text{HO—C—H} \\ | \\ \text{COOH} \\ C \end{array} \longleftarrow \begin{array}{c} \text{CHO} \\ + \\ - \\ \text{CH}_2\text{OH} \\ (19) \end{array}$$

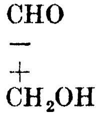
Since mesotartaric acid is known to have the configuration *A*, and the active tartaric acids configurations *B* and *C*, it follows that the erythroses must be

(16) and (17) and the threoses (18) and (19). The erythroses on reduction give *i*-erythritol, the D-threose gives a *lævo-* and the L-threose a *dextro*-rotatory erythritol.

It may be remarked that when D-erythrose and D-threose are written side by side :—

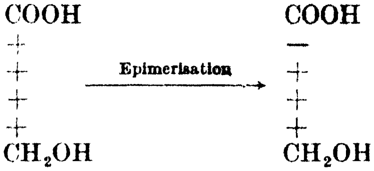


$$\begin{array}{c}CHO\\+\\+\\CH_2OH\end{array}$$



$$\begin{array}{c}CHO\\—\\+\\CH_2OH\end{array}$$

it is seen that they differ only by the sign of the group adjacent to the aldehyde group ; such pairs, however long the molecule, are termed *epimers* provided always that the one point of difference is adjacent to the —CHO group. When a single epimer is converted to the corresponding acid and is boiled with quinoline an equilibrium mixture of the two epimeric acids is formed, and may usually be separated into its constituents by crystallisation. The procedure is of the utmost importance in the elucidation of sugar structures. If an acid, say, for example (20), the structure of which is known, gives another acid on epimerisation, the structure of the second acid must be (21).

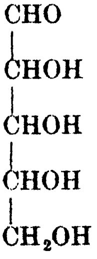


$$\begin{array}{c}COOH\\+\\+\\+\\+\\CH_2OH\end{array} \xrightarrow{\text{Epimerisation}} \begin{array}{c}COOH\\—\\+\\+\\+\\CH_2OH\end{array}$$

(20) (21)

The Aldopentoses

There are seven pentose sugars which correspond to the typical aldose structure (22), and which occur in nature or may be prepared in the laboratory ; they are listed by name in (23) from which it will be evident that *l*-lyxose has



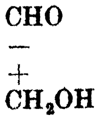
$$\begin{array}{l}CHO\\|\\CHOH\\|\\CHOH\\|\\CHOH\\|\\CH_2OH\end{array}$$

(22)

	1		2		3		4	
D- and L-arabinose	+	—	—	+	+	—	—	+
D- and L-ribose	+	—	+	—	—	+	—	+
D- and L-xylose	+	—	+	—	+	—	+	—
D-lyxose	D-	L-	D-	L-	D-	L-	D-	L-

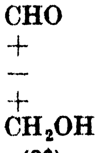
(23) (24)

not yet been obtained. The four enantiomorphic pairs are shown in outline in (24) and our task is first to attach the names of (23) to the configurations in (24). The substance to which the name D-xylose is given yields D-threose when it is degraded to the next lower sugar at the —CHO group end. Since (25) represents D-threose, the structure of D-xylose must be either (26) or (27). On



$$\begin{array}{c}CHO\\—\\+\\CH_2OH\end{array}$$

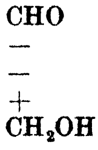
(25)



$$\begin{array}{c}CHO\\+\\—\\+\\CH_2OH\end{array}$$

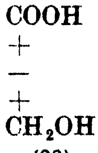
(26)

or



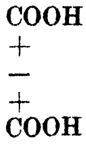
$$\begin{array}{c}CHO\\—\\—\\+\\CH_2OH\end{array}$$

(27)



$$\begin{array}{c}COOH\\+\\—\\+\\CH_2OH\end{array}$$

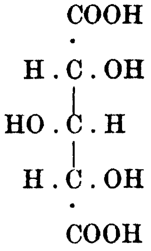
(28)



$$\begin{array}{c}COOH\\+\\—\\+\\COOH\end{array}$$

(29)

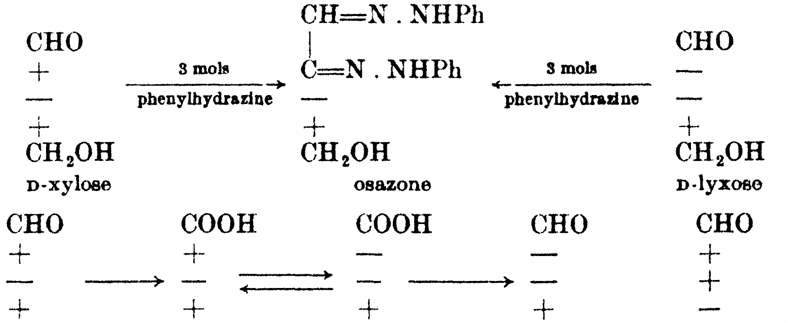
oxidation, D-xylose gives, first by conversion of the aldehyde group to —COOH, a D-xylonic acid and subsequently by oxidation at both ends a xylotrihydroxyglutaric acid. Since the latter is inactive by internal compensation it must have the structure (29). It will be observed this trihydroxyglutaric acid which has been rewritten (30) has only two asymmetric carbon atoms; the centre atom is not asymmetric; the structure of the two remaining active groups must therefore be + in both cases, as in mesotartaric acid. This means, therefore, that D-xylose has the configuration (26).



$$\begin{array}{c} COOH \\ \cdot \\ H.C.OH \\ | \\ HO.C.H \\ | \\ H.C.OH \\ \cdot \\ COOH \end{array}$$

(30)

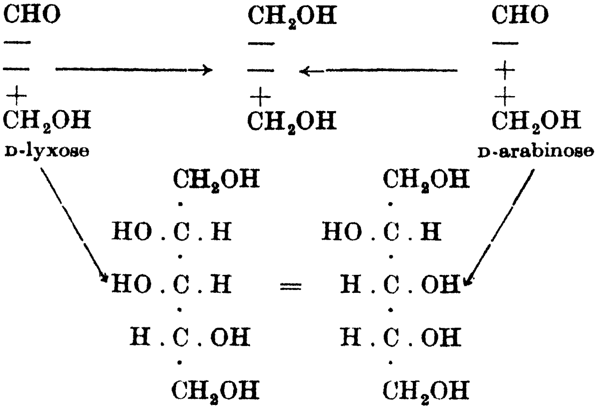
D-Xylose and D-lyxose give the same osazone; this implies that the two sugars are epimers; D-lyxose must, therefore, have the structure (27). This can be confirmed by the conversion of D-xylose into D-lyxose by the process shown in (31). D-Xylose is oxidised to D-xylonic acid (32) which on boiling with quinoline epimerises, giving a mixture of D-xylonic and D-lyxonic acids. If these are separated the D-lyxonic acid lactone can be reduced to D-lyxose (33) with sodium amalgam in weakly acid solution. Although L-lyxose has not yet been isolated, it has been accorded the stereochemical structure (34).



(32) (31) (33) (34)

The sugar, D-arabinose, which has been isolated from certain glycosides, can be reduced to a pentahydric alcohol, D-arabitol; on the other hand, D-lyxose on reduction gives the same alcohol; the full implication of this is seen in the detailed formula (35) in which it is clear that the pentahydric alcohol from D-lyxose when turned upside down, is the corresponding alcohol from D-arabinose. Thus, D-lyxose and D-arabinose differ only in that the former has —CHO where the latter has —CH_2OH and *vice versa*. This gives (36) as the structure of D-arabinose, a conclusion which is reinforced by the fact that D-lyxose and D-arabinose both give the same D-trihydroxyglutaric acid, thus indicating a stereo-identical core.

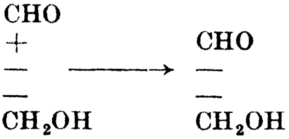
L-Arabinose (37), when degraded to the next lowest aldose, gives L-erythrose, (38), thus confirming its structure as the inversion of D-arabinose.



(36)

(35) D-arabitol

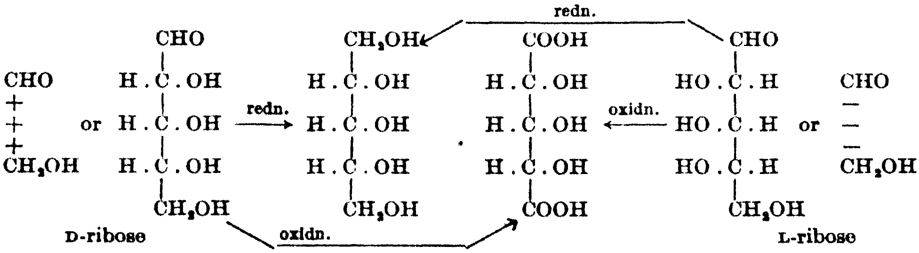
The remaining pair of structures (1 in formula 24) must, by elimination, belong to D- and L-ribose, but additional confirmation of this lies in the fact



(37) L-arabinose

(38) L-erythrose

that both D- and L-ribose (39 and 40) give on reduction the inactive, internally compensated pentahydric alcohol, adonitol (41), and on oxidation the similarly internally compensated ribotrihydroxyglutaric acid (42).



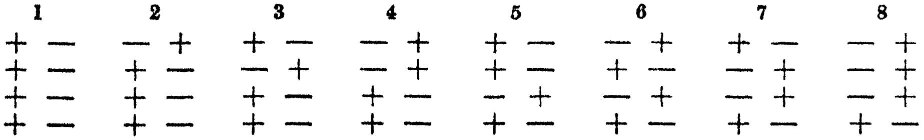
(39) (41) (42) (40)

The structures of all the aldopentoses have, therefore, been elucidated.

ALDOHEXOSES

The sixteen possible structures for the aldo-hexoses are written in (43): there are, of course, eight pairs which correspond to the natural and synthetic aldohexose sugars :—

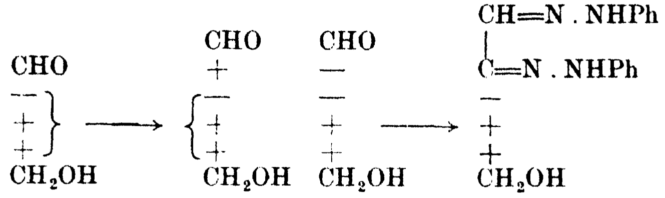
1. D- and L-allose
2. D- and L-altrose
3. D- and L-glucose
4. D- and L-mannose
5. D- and L-gulose
6. D- and L-idose
7. D- and L-galactose
8. D- and L-talose



(43)

The attachment of these formulæ to their respective names is carried out by a series of arguments, similar in many ways to those used in the case of the pentoses. The following steps are useful in obtaining a clear picture of the various structures.

(1) Two hexoses, D-glucose and D-mannose give D-arabinose (44) when degraded to the corresponding pentose. Since the structure of arabinose is known then both D-glucose and D-mannose must have the same structure in the lower three units of the active core; they must, in fact, be epimers of the structure (45). This is confirmed by the fact

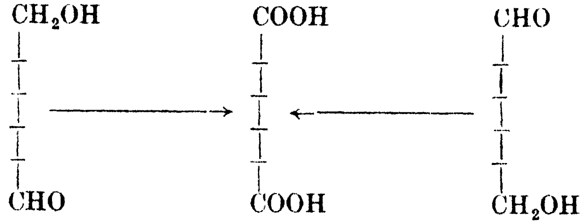


(44) D-arabinose

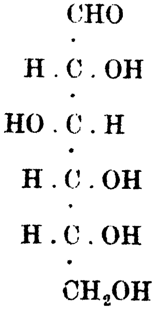
D-glucose and D-mannose (45)

(45*a*)

that they both give the same osazone (45*a*). To decide which of the two formulæ represent glucose, and which mannose, attention must be turned to the sugar, L-gulose, which gives on oxidation the same acid (D-saccharic acid) as glucose. Clearly this is due to the fact that both gulose and glucose contain the same active core, but that the —CHO and — CH_2OH are at reverse ends, thus :—

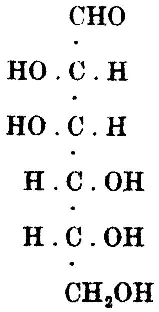


Referring again to formula (45), it is clear that only one core (the first of the pair) could give two different sugars by reversing the ends; this structure must therefore belong to D-glucose. Thus, the structures of D-glucose, D-mannose and L-gulose must be (46), (47) and (48). At the



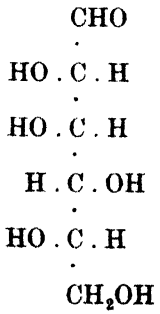
$$\begin{array}{c} CHO \\ H\cdot C\cdot OH \\ HO\cdot C\cdot H \\ H\cdot C\cdot OH \\ H\cdot C\cdot OH \\ CH_2OH \end{array}$$

(46)



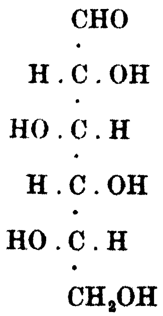
$$\begin{array}{c} CHO \\ HO\cdot C\cdot H \\ HO\cdot C\cdot H \\ H\cdot C\cdot OH \\ H\cdot C\cdot OH \\ CH_2OH \end{array}$$

(47)



$$\begin{array}{c} CHO \\ HO\cdot C\cdot H \\ HO\cdot C\cdot H \\ H\cdot C\cdot OH \\ HO\cdot C\cdot H \\ CH_2OH \end{array}$$

(48)

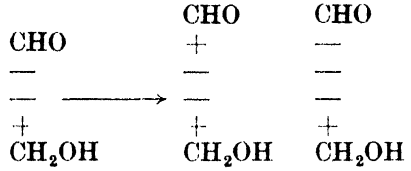


$$\begin{array}{c} CHO \\ H\cdot C\cdot OH \\ HO\cdot C\cdot H \\ H\cdot C\cdot OH \\ HO\cdot C\cdot H \\ CH_2OH \end{array}$$

(49)

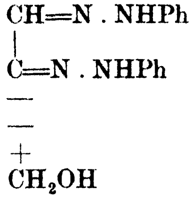
same time, since L-gulose and L-idose are epimers, the latter must have the structure (49). This disposes of four of the eight pairs of structurally different aldo-hexoses.

(2) D-Galactose and D-talose give D-lyxose on degradation, and have the same osazone (51). They are, therefore, epimers, and are expressed by the formulæ (50).



D-lyxose D-galactose and D-talose

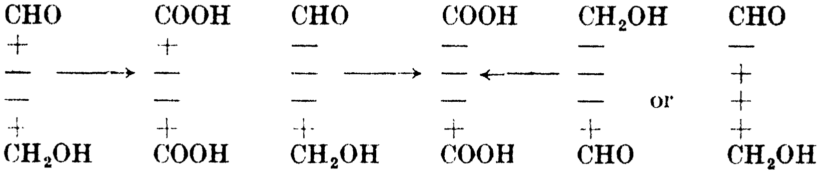
(50)



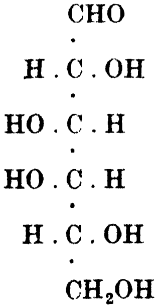
D-galactosazone

(51)

(3) If we consider the oxidation of the two structures which represent D-galactose and D-talose, we find that two different acids are produced; one from galactose is mucic acid (an internally compensated acid) which must therefore have the structure (53), and a second from *d*-talose is D-talomucic acid, which is optically active and has the structure (54). D-Galactose, D-talose and D-altrose have, therefore, the structures (56), (57) and (58), and since D-altrose and D-talose yield the same talomucic acid, they must be related by the principle of core-inversion; since D-allose and D-altrose are epimeric the structures of all eight pairs of aldohexoses is known. The structures of D-allose and D-altrose are confirmed by the fact that an epimeric mixture of these two sugars is obtained by converting D-ribose into an aldohexose.



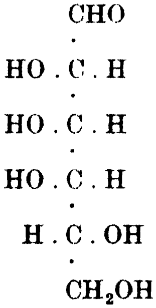
(52) Mucic acid (53) D-talomucic acid (54) (55)



$$\begin{array}{c} CHO \\ H.C.OH \\ HO.C.H \\ HO.C.H \\ H.C.OH \\ CH_2OH \end{array}$$

(56)

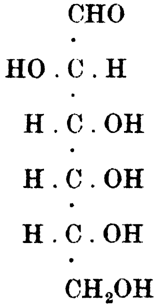
D-galactose



$$\begin{array}{c} CHO \\ HO.C.H \\ HO.C.H \\ HO.C.H \\ H.C.OH \\ CH_2OH \end{array}$$

(57)

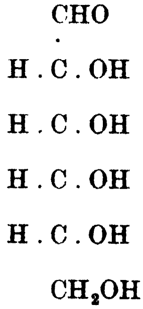
D-talose



$$\begin{array}{c} CHO \\ HO.C.H \\ H.C.OH \\ H.C.OH \\ H.C.OH \\ CH_2OH \end{array}$$

(58)

D-altrose



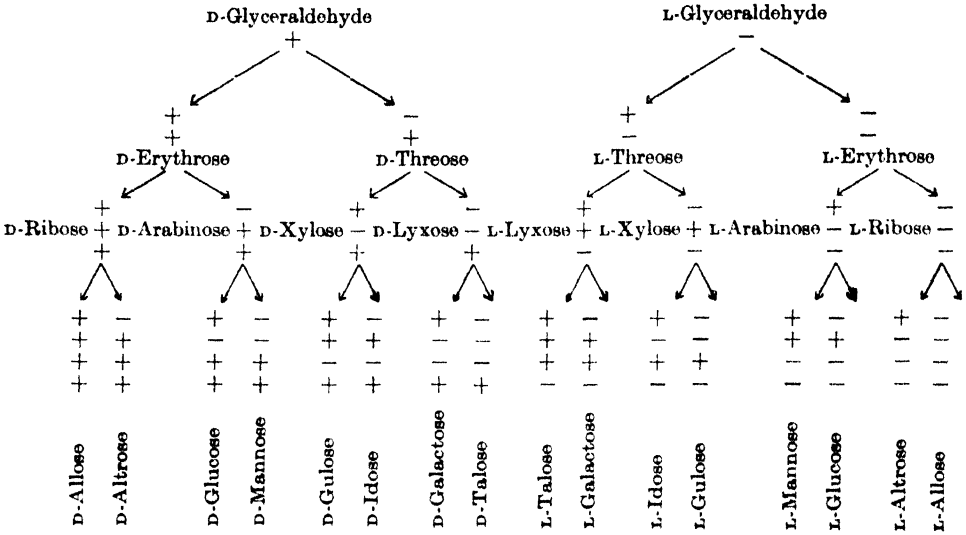
$$\begin{array}{c} CHO \\ H.C.OH \\ H.C.OH \\ H.C.OH \\ H.C.OH \\ CH_2OH \end{array}$$

(59)

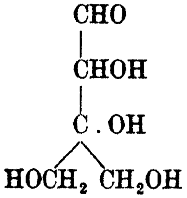
D-allose

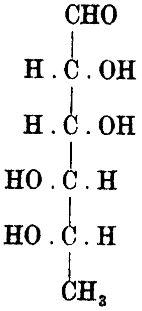
The whole of these structures and their logical development from the D- and glyceric aldehydes is summarised in Table I. It is only fair to add that the arguments which have been developed in the previous pages for the assignment of structures to the aldose sugars are not arranged chronologically; in some cases the structures of the smaller sugars were inferred from those of the larger and the structural knowledge which appears above to proceed quite easily from smaller to larger aldoses may have been acquired subsequently to the establishment of the larger structure by laborious roundabout means. Nothing has yet been said about the reactions used in the development of this subject or the character of the substances themselves; these matters will be discussed after the structural difficulties have been disposed of.

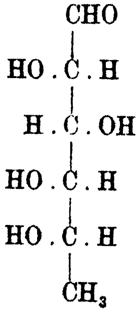
TABLE I. ALDOSE SUGARS

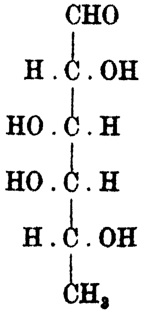


The series already enumerated does not entirely exhaust the possibilities in the aldose group of sugars; one or two branched and alkyl-substituted natural sugars are known. The chief of these are shown in outline formula below :—


Apiose
(60)


L-Rhamnose
(61)


L-iso-Rhamnose
(62)


D-Fucose
(63)

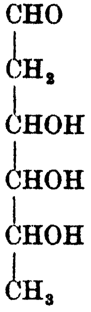
Votoček[1] has proposed to call the methyl pentoses according to the hexoses from which they are derived, e.g.,

Rhamnose = Mannomethylose
iso-Rhamnose = Glucomethylose
Fucose = Galactomethylose

---

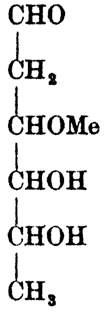
[1] Votoček and Rác, *J. Czech. Chem. Comm.*, 1929, 4, 239.

This method has an advantage in linking up the methyl pentoses in such a way that their structure can be easily correlated, and will serve for new sugars ; the names rhamnose and fucose, however, are too firmly fixed to be altered.



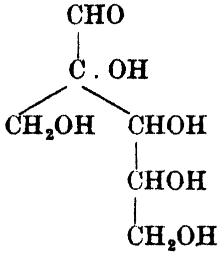
$$\begin{array}{l}\mathrm{CHO}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_3}\end{array}$$

(64)

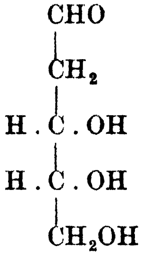


$$\begin{array}{l}\mathrm{CHO}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CHOMe}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_3}\end{array}$$

(65)



(66)



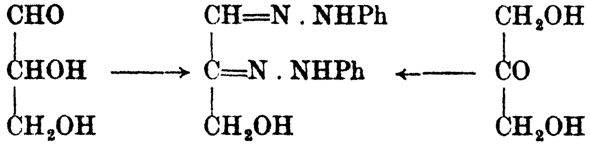
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{H\,.\,C\,.\,OH}\\ |\\ \mathrm{H\,.\,C\,.\,OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

(67)

Mention must also be made of digitoxose (64) and cymarose, its 3-methyl ether (65), which represent yet another type of aldose, namely methyl pentoses with a desoxy group next to the —CHO group. A similar sugar, found in animal nucleic acids is desoxy-D-ribose (67) called ' thymose '. The branched structure of apiose is found also in hamamelose (66) and synthetic sugars with elongated —CH(OH)— chains have been made up to the decoses with ten carbon atoms ; very few of the family are met with in natural conditions ; an exception is the seven carbon sugar sedoheptose from *Sedum spectabile.*

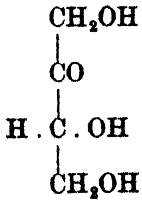
THE KETOSES

Dihydroxyacetone, CH_2OH . CO . CH_2OH, usually obtained by the fermentation of glycerol by sorbose bacteria, has no problem of structure as it contains no asymmetric carbon atom, and does not exhibit any possibilities of geometrical variation. Nevertheless, it behaves as a ' sugar ' in solution, giving the same osazone as glyceric aldehyde :



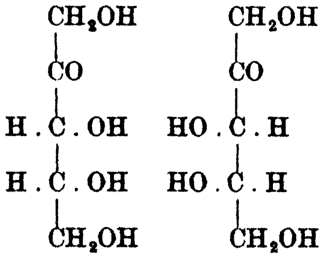
$$\begin{array}{lcllcl}\mathrm{CHO} & & \mathrm{CH{=}N\,.\,NHPh} & & \mathrm{CH_2OH}\\ | & & | & & |\\ \mathrm{CHOH} & \longrightarrow & \mathrm{C{=}N\,.\,NHPh} & \longleftarrow & \mathrm{CO}\\ | & & | & & |\\ \mathrm{CH_2OH} & & \mathrm{CH_2OH} & & \mathrm{CH_2OH}\end{array}$$

In the solid form it is dimeric and melts at 80°.



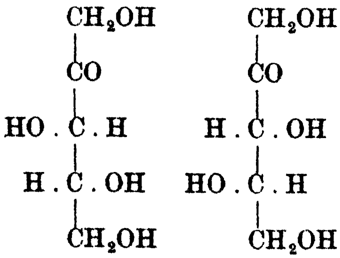
$$\begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{CO}\\ |\\ \mathrm{H\,.\,C\,.\,OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-Erythrulose
(68)



$$\begin{array}{cc}\mathrm{CH_2OH} & \mathrm{CH_2OH}\\ | & |\\ \mathrm{CO} & \mathrm{CO}\\ | & |\\ \mathrm{H\,.\,C\,.\,OH} & \mathrm{HO\,.\,C\,.\,H}\\ | & |\\ \mathrm{H\,.\,C\,.\,OH} & \mathrm{HO\,.\,C\,.\,H}\\ | & |\\ \mathrm{CH_2OH} & \mathrm{CH_2OH}\end{array}$$

D- and L-Riboketose
(69)



$$\begin{array}{cc}\mathrm{CH_2OH} & \mathrm{CH_2OH}\\ | & |\\ \mathrm{CO} & \mathrm{CO}\\ | & |\\ \mathrm{HO\,.\,C\,.\,H} & \mathrm{H\,.\,C\,.\,OH}\\ | & |\\ \mathrm{H\,.\,C\,.\,OH} & \mathrm{HO\,.\,C\,.\,H}\\ | & |\\ \mathrm{CH_2OH} & \mathrm{CH_2OH}\end{array}$$

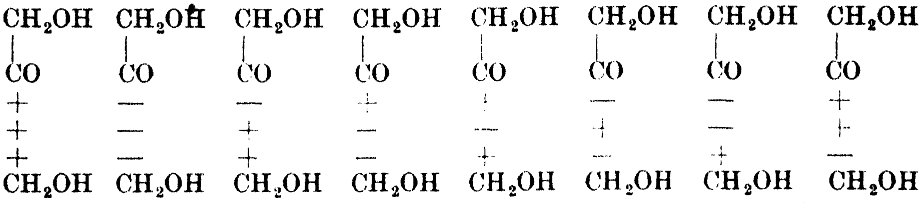
D- and L-Xyloketose
(70)

There is also but one ketotetrose, but it can exist in two optically active forms by virtue of its single asymmetric carbon atom ; it is called ' erythrulose '. Ketopentoses, of which four should exist, are little known ; one, L-xyloketose

(70), has been isolated from natural sources (pentosic urine), although it has been conjectured that one of the pentoses formed during the autocondensation of formaldehyde to give formose, is the D-riboketose (69), and its L-isomer.

THE KETOHEXOSES

Of the four possible pairs of ketohexoses shown by the configurations below, members of each pair are known and the structures represent D- and L-fructose, D- and L-sorbose, D- and L-tagatose and D- and L-psicose. The assignment of structure is a comparatively easy matter once the structures of the aldohexoses are known, since each ketohexose gives an osazone identical with one from a pair of aldohexoses, thus.—

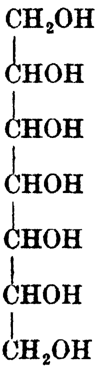

(A) (B) (C) (D)

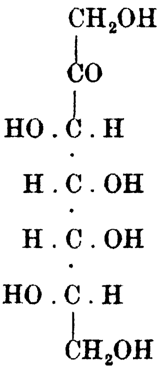
(71)

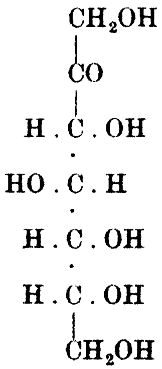
D-Fructose gives D-glucosazone and has structure B (71).
D-Sorbose gives D-gulosazone and has structure C (71).
D-Tagatose gives D-galactosazone and has structure D (71).

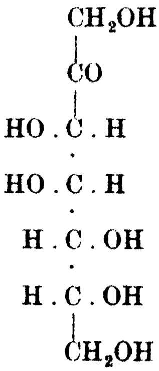
leaving structure A for psicose.

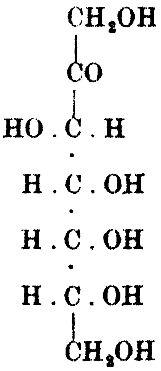
The higher ketose sugars have been examined by Bertrand; from perseitol (72) (a vegetable heptitol) he obtained two sugars,[1] perseulose (73) and D-glucoheptulose (74). A mannoketoheptose has been isolated from the avocado pear (75), and reference has already been made to the sedoheptose (76) from *Sedum spectabile*.


(72)


(73)


(74)


(75)


(76)

RING STRUCTURE IN THE SUGARS

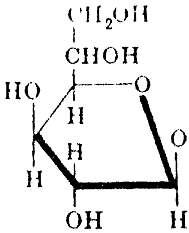
Hitherto, no account has been taken of ring formation in the sugar family; all previous examples have been treated as though they were open-chain polyhydroxy aldehydes or ketones, and whilst it is clear from their general reactions that the simple sugars can behave as such, there is much evidence which points to the existence of cyclic forms. The first hint of this was the suggestion made by Colley[1] in 1870 to explain unusual properties of a nitroacetylglucose. Skraup[2] showed that glucose penta-acetate has no aldehyde group, and in 1889 Erwig and Koenigs[3] showed that there were two glucose penta-acetates and proposed a ring structure to explain their existence. Fischer's observation[4] in 1893 that D-glucose did not give a normal acetal but that only one methyl group entered the structure was a further extension of this idea. Two

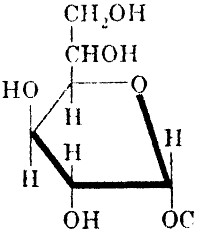
---

[1] Bertrand and Nitzberg, *C.R.*, 1928, **186**, 1172; Bertrand, *Bull. Soc. Chim.*, 1909, [4] **5**, 629.

α-methyl-D-glucoside	$[\alpha]_D$ + 159°
β-methyl-D-glucoside	$[\alpha]_D$ − 34°

products were produced, and Fischer correctly interpreted them as ring isomers, but arbitrarily accorded them a furan structure, (77) and (78), afterwards shown to be incorrect.


(77)


(78)

So far, it may appear that although methyl-D-glucoside exhibits two forms, this has not much bearing on the structure of glucose itself. The extension of these ideas to glucose depends on three main points :—

(1) A consideration of mutarotation.
(2) Tanret's isolation of α- and β-glucose.
(3) Armstrong's direct relation of the two forms of glucose to the α- and β-methyl glucosides.

All simple sugars show mutarotation, namely the gradual alteration of the optical rotatory power of freshly made solutions to a constant minimum or maximum. Much discussion of this phenomena centred around the suggestion that there were two forms of glucose and that the alteration of rotatory power is due to the conversion of one form to an equilibrium mixture of the two. The isolation by Tanret[5] in 1895 of the two forms :—

α-D-glucose	$[\alpha]_D$ + 113°
β-D-glucose	$[\alpha]_D$ + 19°

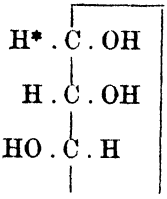
and the demonstration of the fact that either form in solution mutarotates to $[\alpha]_D$, + 52·5°, finally clinches the matter, and demonstrates that the sugar D-glucose exists in two distinct forms. Armstrong[6] followed the hydrolysis of α-methyl-D-glucose by maltase polarimetrically and observed the formation of α-D-glucose, of high rotatory power, and in similar experiments on the hydrolysis of β-methyl-D-glucose with emulsin showed the formation of β-glucose. Behrend and Roth[7] acetylated the α- and β- forms of D-glucose in pyridine and obtained

	penta-acetyl-α-glucose	$[\alpha]_D$ + 102° ($CHCl_3$)
and	penta-acetyl-β-glucose	$[\alpha]_D$ + 4° ($CHCl_3$).

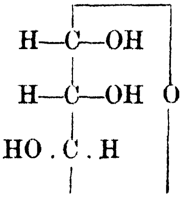
[1] Colley, *Ann. Chim. Phys.*, 1870, [4] **21**, 363.
[2] Skraup, *Monatsh.*, 1889, **10**, 401.
[3] Erwig and Koenigs, *Ber.*, 1889, **22**, 2207.
[4] Fischer, *ibid.*, 1893, **26**, 2400.
[5] Tanret, *Bull. Soc. Chim.*, 1895, [3] **13**, 728.
[6] Armstrong, *J.C.S.*, 1903, **83**, 1305.
[7] Behrend and Roth, *Ann.*, 1904, **331**, 359.

All the above facts throw no light on the two fundamental questions of (*a*) the orientation of the groups attached at the new asymmetric carbon atom (* in 79) and (*b*) the exact nature of the ring.

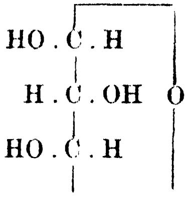
It cannot be said that the evidence for the configuration of the '1'-carbon atom and its group is very convincing. Böeseken[1], from observations on simpler polyhydroxy compounds arrived at the conclusion that a *cis*- glycol structure as in (80) gave a stronger acid than the corresponding *trans*- structure when combined with boric acid. Experiment revealed that a solution of α-D-glucose in aqueous boric acid decreased in conductivity during mutarotation and the formation of β-D-glucose. On the other hand, during the mutarotation of β-D-glucose in aqueous solutions of boric acid the conductivity increased. This would indicate that (80) is α-D-glucose, and (81) β-D-glucose. Whilst no rigid chemical method has been devised to confirm this conclusion, it has not been shown to conflict with the general behaviour of α- and β-D-glucose in other respects.



(79)

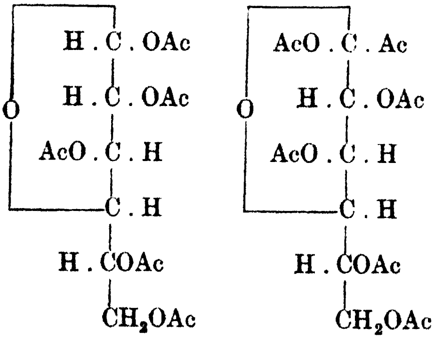


(80)
α-D-glucose

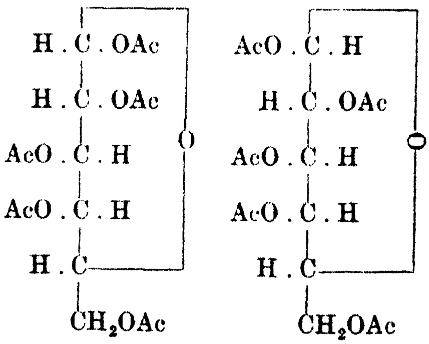


(81)
β-D-glucose

Insofar as the nature of the ring is concerned, Fischer arbitrarily assigned the furanose structure to glucose, and it was not until Hudson[2] and his co-workers, over 20 years later, isolated four isomers of the penta-acetate of D-galactose, that attention became focussed on the matter again. The four penta-acetates of D-galactose are divisible into two α-β pairs, and each pair differs in respect of the size of the ring, one pair containing a furanose and the other a pyranose structure :—



α-D- β-D-
Furanose structure



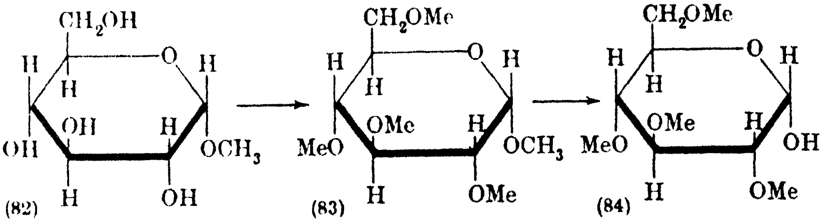
α-D- β-D-
Pyranose structure

although this was not proved for some time after the work referred to. In 1927, Schlubach and Huntenberg[3] obtained the four corresponding penta-benzoyl-D-glucoses, but by this time the work of Purdie, Haworth, Hirst and Irvine had shown that methylation was the key with which the ring-structure of the sugars could be unlocked.

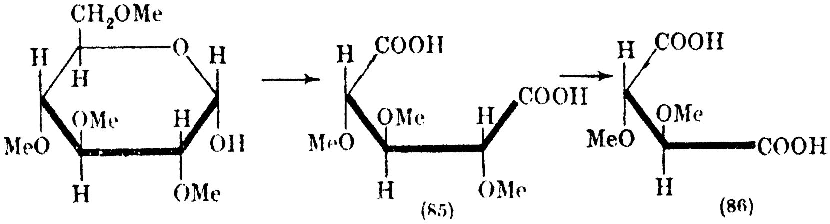
---

[1] Böeseken, *Ber.*, 1913, **46**, 2612.
[2] Hudson *et al.*, *J.A.C.S.*, 1915, **37**, 1589 ; 1916, **38**, 1223.
[3] Schlubach and Huntenberg, *Ber.*, 1927, **60**, 1487.

Purdie and Irvine[1] were at work on this problem at the commencement of the century, long before Hudson had obtained his four penta-acetyl D-galactoses, and in 1903 had published results on the methylation of α-methyl-D-glucose (82), which they achieved by the use of methyl iodide and silver oxide on alcoholic solutions of the glycoside. They found that a tetramethyl-α-methyl-D-glucoside (83) could be obtained. This was readily hydrolysed in dilute acid solution to tetramethyl glucose (84). The great value of this process lies in the fact that the four methyl groups in the final tetramethylglucose may reasonably be supposed to occupy the positions of the free hydroxyl groups of glucose itself. Since the methylated sugars are often crystalline substances which can be distilled in high vacuum without change, many operations and degradations can be carried out with them which would be impossible with the sugars themselves; further, the degradations lead to simpler substances, the structure of which is known, and which by the position of their methyl groups act as indicators to the position of such groups in the parent sugars. Thus, the original tetramethyl-α-methyl-D-glucoside of Purdie distils unchanged *in vacuo*, and yields a beautifully crystalline tetramethyl D-glucose on hydrolysis. When Hirst[2] submitted this tetramethyl-glucose to oxidation with nitric acid, he found an inactive (internally compensated) trimethoxyglutaric acid (85), which indicates that the original tetramethylglucose must still retain the + — + configuration on the 2, 3 and 4 carbon atoms and points strongly to the pyranose ring (1, 5). The fact, also observed by Hirst, that *dextro*-dimethyltartaric acid (86) is also produced confirms this conclusion without adding fresh evidence.



(82) α-Methyl-*d*-glucose (83) Tetramethyl α-methyl-*d*-glucoside (84) Tetramethyl-*d*-glucose



(85) (86)

FURANOSE RING STRUCTURE

If D-glucose is allowed to stand in a methanol solution of hydrogen chloride the methylglycoside of D-glucofuranose is formed; it is difficult to obtain the compound in the solid state, but Fischer[3] obtained considerable data on this furanose which he called a "γ-sugar" (the previously isolated methyl-D-glycosides being from α- and β-glucose). The arguments leading to the recognition of the furanose structure are somewhat complex, and depend on a study of the acetone derivatives of D-glucose. All the formulæ connected with the subject are shown in Table II; they are depicted as though the furanose ring was flat—in the plane at right angles to the paper; D-groups have the —OH below the ring; in L-groups it lies above.

---

[1] Purdie and Irvine, *J.C.S.*, 1903, **83**, 1021.

[2] Hirst, *ibid.*, 1926, 350.

[3] Fischer, *Ber.*, 1914, **47**, 1982.

When two molecules of acetone react with glucose in slightly acid solution diacetoneglucose (87) is formed. The mode of combination of the acetone with the sugar is by loss of two atoms of hydrogen, one from each of two hydroxyl groups (from glucose) and an atom of oxygen from acetone; the substance obtained is, therefore, a cyclic acetal. It is assumed, from evidence which will be adduced later that the pyranose form of D-glucose is converted by opening of the ring followed by closure in the 1, 4-position (88). The action of acetone was first thought to be located at pairs of adjacent —CHOH groups, but although in actual fact the groups in diacetoneglucose are so situated, the implication that acetone is able to form cyclic acetals only with 1, 2- dihydroxy bodies is wrong, as the work of Hibbert on the cyclic acetals of glycerol shows.

When subjected to controlled hydrolysis, diacetoneglucose yields a monoacetoneglucose (89), which does not react with phenylhydrazine or give an osazone. This shows that the '2' carbon atom must be involved. On the other hand, when monoacetoneglucose is methylated it yields a trimethylacetoneglucose (90) which gives a trimethylglucose on removal of the acetone group. Diacetoneglucose on methylation gives a monomethyl dervative (91), which on removal of the acetone gives a crystalline monomethyliglucose (92); this latter gives an osazone, from which fact it is deduced that the acetone residue in monoacetoneglucose (and, of course, one of the acetone residues in diacetoneglucose) is attached to the '1' and '2' carbon atoms.

The crystalline monomethylglucose proved to be the 3-methyl compound, as was shown by an exceedingly ingenious device of Freudenberg and Doser,[1] who formed the *p*-toluenesulphonic ester of diacetoneglucose and by hydrolysing this with hydrazine obtained 3-hydrazino diacetoneglucose (93), during the hydrolysis of which a pyrazole derivative (94) was formed identified by the formation of pyrazole-3-carboxylic (95) acid on oxidation. This pyrazole ring formation indicates that the 'free' hydroxyl in diacetoneglucose is in the '3' position.

Confirmation was obtained by Levene and Meyer's[2] conversion of monomethylglucose to a crystalline monomethylglucoheptonic lactone (96) in which the free hydroxyl group is inferred to be in the L- position from an application of Hudson's rule (see Vol. III, Chap. IV). In this way the structural arrangement of the first three carbon atoms is determined. The configuration of the remainder was decided from consideration of the trimethyl-D-glucose obtained from the methylation of monoacetone-D-glucose and removal of the acetone group. Full methylation with methyl sulphate and alkali[3] gave a tetramethyl-α-methyl-D-glucoside (97) which readily hydrolysed by loss of a methyl group at the '1' position to give a tetramethyl-D-glucose (98). That this substance was the 2, 3, 5, 6-tetramethylglucose was established by Haworth and his coworkers[4] by oxidation to 2, 3, 5, 6-tetramethylgluconic acid, the lactone of which (99) crystallises readily, and may be progressively degraded to give recognisable 4- and 5-carbon acids. The establishing of the structure of this compound as a 2, 3, 5, 6-tetramethyl derivative, taken together with previous evidence makes it obvious that the ring of glucose in its diacetone compound is in the 1, 4-position. The sugar itself is usually referred to as D-glucofuranose.

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[1] Freudenberg and Doser, *Ber.*, 1923, **56**, 1243.

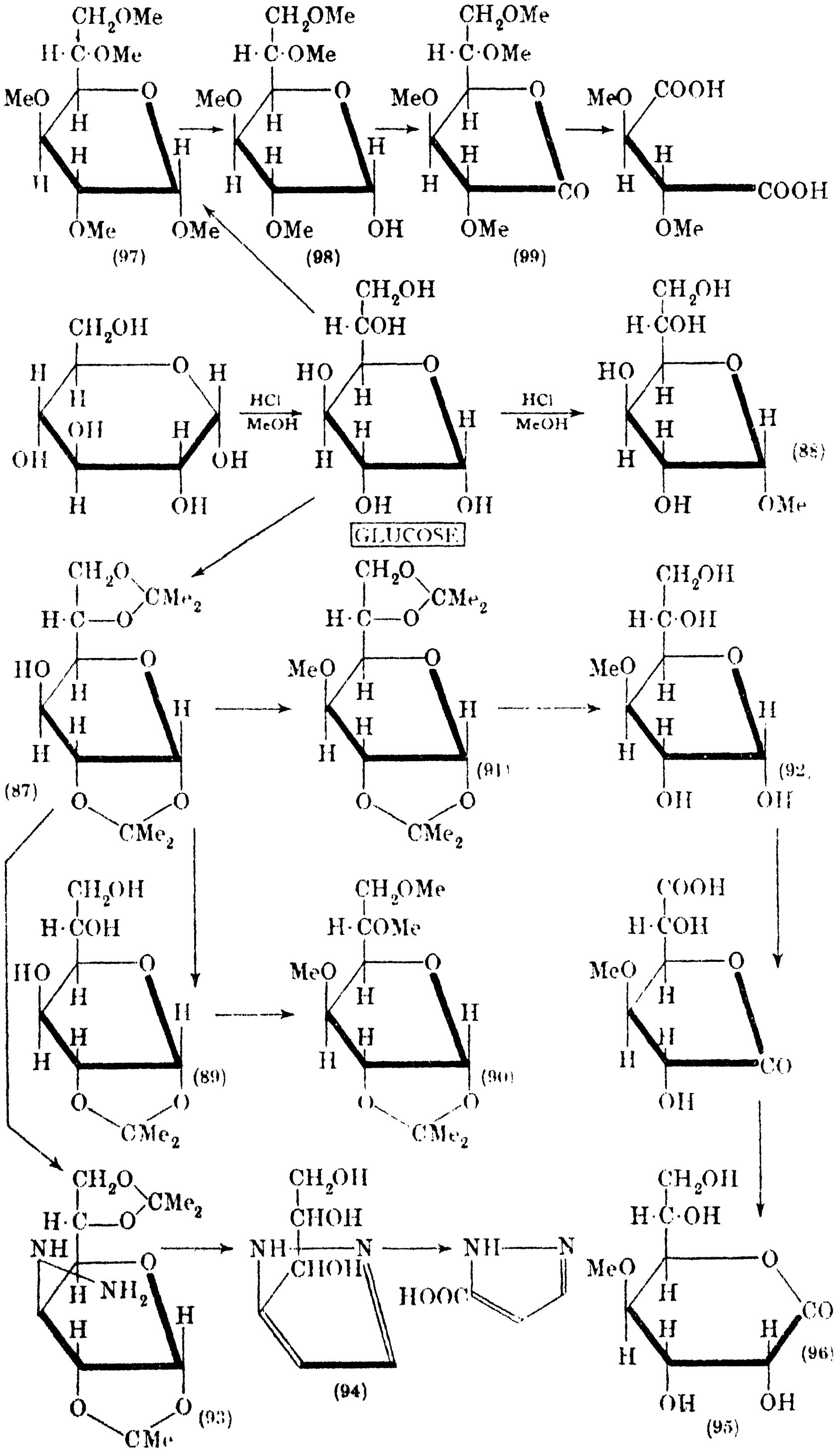
[2] Levene and Meyer, *J. Biol. Chem.*, 1922, **54**, 805.

[3] Michoel and Hess, *Ann.*, 1926, **450**, 21.

[4] Anderson, Charlton and Haworth, *J.C.S.*, 1929, 1329.

TABLE II

SOME DERIVATIVES OF D- GLUCOFURANOSE

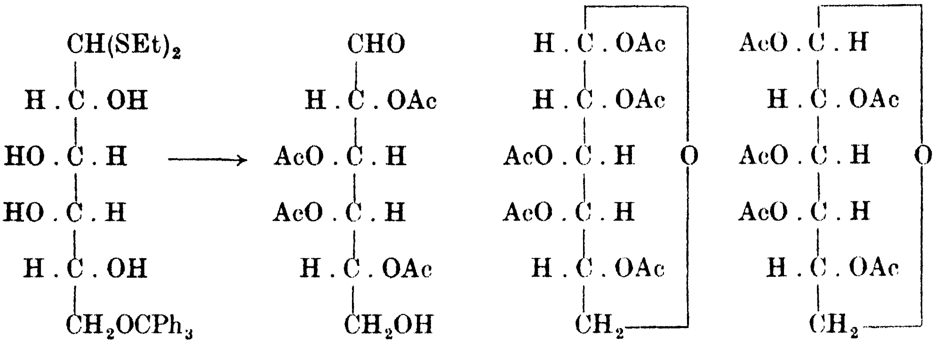


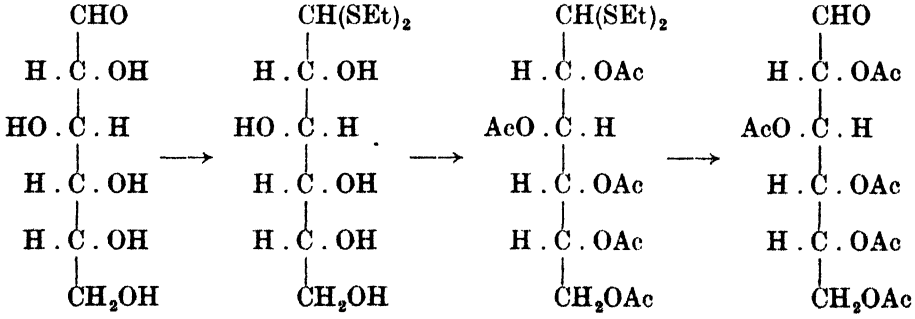
The evidence set out above shows that there are four varieties, at least, of D-glucose, namely :—

α-D-glucopyranose
β-D-glucopyranose
α-D-glucofuranose
β-D-glucofuranose

there will also be a similar set of four L-glucoses.

In general the furanose sugars are very labile, and when prepared in solution readily revert to the more usual pyranose form. There is, however, reason to believe that the ring-forming capabilities of the 'simple' aldoses are by no means exhausted by the development of pyranose and furanose structures; Micheel and his school,[1] obtained yet another pair of acetyl derivatives of D-galactose, in which methylation studies indicate the presence of a 1, 6- ring. They protected the aldehyde group of D-galactose by allowing it to combine with ethyl mercaptan, and the —CH_2OH group by etherifying it with triphenyl carbinol producing the substance (100) which was acetylated; the tetra-acetyl derivative can be so treated as to remove the mercaptal- and trityl-groups without disturbing the acetylation, thus freeing the terminal —CHO and —CH_2OH groups and producing 2, 3, 4, 5-tetra-acetyl-D-galactose (101) which, on further acetylation, gives the two compounds, α- and β-penta-acetyl-galacto-heptanose (102).


(100) (101) α- β-
penta-acetyl-D-galactoheptanose
(102)


(103) (104) (105) (106)

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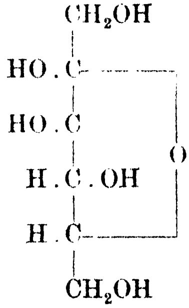
[1] Micheel *et al.*, *Ann.*, 1933, **502**, 85; 1933, **507**, 133; *Ber.*, 1933, **66**, 1957; 1934, **67**, 1665.

So much has been said in previous pages about the ring forms of glucose that the aldehyde nature of its open-chain form is apt to have been almost forgotten ; the acyclic form is, however, a very real entity, and many characteristic 'sugar' reactions are concerned with the —CHO group of acyclic D-glucose. The isolation by Wolfrom[1] of a crystalline acyclic penta-acetyl-D-glucose in which the aldehyde function was preserved intact, not only added another to the lengthening list of penta-acetyl derivatives, but also gave a further proof of the validity of the structures proposed for the previously discovered types. Wolfrom allowed glucose to react with ethyl mercaptan, giving the mercaptal (104) which can be acetylated to a penta-acetyl derivative (105) which, in turn, gives the aldehydo-penta-acetate (106).

TABLE III.

d-GALACTOSE PENTA-ACETATES.

Penta-acetyl derivative from	Ring	M.P.	$[\alpha]^{D}_{20^\circ}$ ($CHCl_3$)
α-D-Galactofuranose . .	5	87°	+ 61°
β-D-Galactofuranose . .	5	98°	— 42°
α-D-Galactopyranose . .	6	96°	+ 107°
β-D-Galactopyranose . .	6	142°	+ 23°
α-D-Galactoheptanose . .	7	128°	— 11°
β-D-Galactoheptanose . .	7	112°	— 103°
Aldehydo-D-galactose . .	nil	121°	— 25°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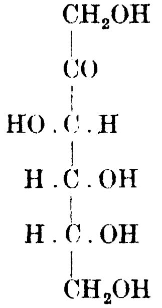
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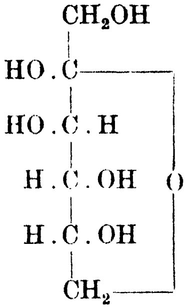
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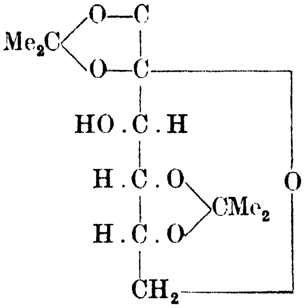
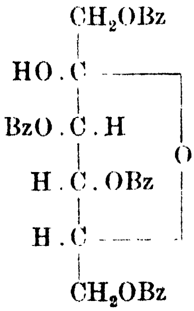

(110)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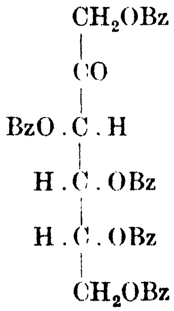
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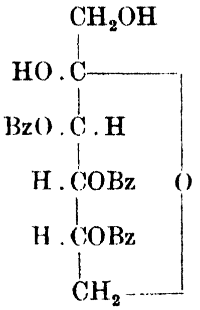
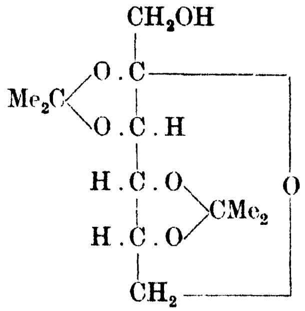

(113)


(114)

The removal of the = $(SEt)_2$ groups is effected by allowing a dilute acetone solution of the mercaptal to react with aqueous mercuric chloride in the presence of cadmium carbonate. Such open-chain or 'aldehydo' sugars have been prepared from several aldohexoses, including D-galactose of which seven penta-acetyl derivatives are known ; their properties are summarised in Table III.

---

[1] Wolfrom, *J.A.C.S.*, 1929, **51**, 2188.

The various forms which have been described for glucose and galactose are paralleled by similar ring structures in the case of many other aldohexoses, but in the case of the sugars talose, idose, altrose, etc., scarcity of experimental material has prevented the full investigation of ring structure. Little is known of the ring structures of aldopentoses, although Swan and Evans[1] have isolated an α-methyl-D-trimethylarabinoside.

With ketose sugars, such as fructose, ring formation exists, but is less completely investigated than with the aldoses. Extensive work by Brigl and Schinle[2] has shown that when D-fructose is benzoylated, three products are formed, two tetrabenzoyl derivatives and a pentabenzoyl compound. The latter still preserves its keto- group intact and must, therefore, be the acyclic substance (112) derived from keto-fructose (108).

Space does not permit a full account of the arguments which led Brigl and Schinle to propose that the tetrabenzoyl derivatives are derived from the D-fructofuranose and D-fructopyranose structures respectively (107) and (109). There are also two isomeric di-acetone fructoses which are both formed from D-fructose, and may be separated by fractional crystallisation; methylation studies indicate that they are the 1, 2, 4, 5-compound (110) and the 2, 3, 4, 5-compound (114) respectively; but this suggestion lacks rigid confirmation.

SOME CHEMICAL REACTIONS AMONG THE SIMPLE SUGARS

In the foregoing discussion of the structure of simple sugars, as little as possible has been said about the means of achieving chemical transformations in order not to distract the reader's attention from constitutional problems. It is proposed now to deal with the various reactions that the simple aldoses and ketoses can undergo.

In the first place, they will undergo almost all the reactions which are commonly associated with the aldehydes or ketones. Thus, semicarbazones and compounds with phenylhydrazine can be obtained; indeed, it was in connection with the elucidation of sugar structures that Emil Fischer developed the chemistry of aryl hydrazines. When a simple aldose or ketose (D-glucose or D-fructose, in the example below) reacts with phenylhydrazine, a phenylhydrazone (115*b*) and (115*c*), is first formed. A second molecule then oxidises an adjacent —CHOH or —CH_2OH group to —CO or —CHO with which a third molecule of phenylhydrazine combines yielding an 'osazone' or '*bis*-phenylhydrazone'; D-glucose and D-fructose both give the same product, written (115*d*) for many years, but which was shown by the Percivals[3] in 1935 to have the fructopyranose structure (115*e*). These investigators methylated glucosazone, obtaining a trimethyl derivative which on removal of the hydrazine groups and reduction of the aldehyde group yielded 3, 4, 5-trimethylfructose (115*f*).

By removing the two phenylhydrazine residues from glucosazone, a keto-aldose is obtained. Fischer called such a sugar an 'osone', and in the case cited it would be 'D-glucosone'. The nominal straight-chain formula (115*g*) is often used for D-glucosone, but it is very probable that the pyranose form (115*h*) is more common; this point has not, however, been finally settled. The osone when reduced gives D-fructose, so that the procedure constitutes a method of passing from an aldose to a ketose sugar.

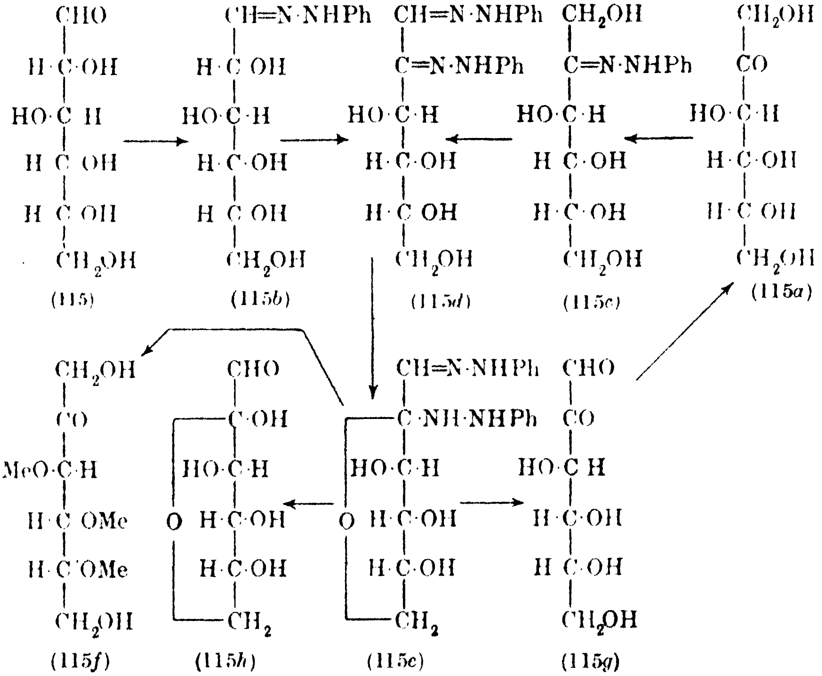
In general, the osazones form a useful and convenient group of substances for isolating and characterising sugars. As a rule, they are crystalline, and much less soluble than the sugars from which they are derived. The characteristic crystalline form of an osazone under the microscope often enables small amounts of sugars to be recognised. An extension of the method is the use of 1-methyl-1-phenylhydrazine for the differentiation of aldoses and ketoses. Owing to steric factors, methylphenylhydrazine only gives the colourless hydrazone with an aldose; with a ketose, the yellow osazone is formed.

---

[1] Swan and Evans, *J.A.C.S.*, 1935, **57**, 200.

[2] Brigl and Schinle, *Ber.*, 1933, **66**, 325; 1934, **67**, 127.

[3] E. E. Percival and E. G. V. Percival, *J.C.S.*, 1935, 1398.



The reducing properties of simple sugars are well developed, and the use of Fehling's and Benedict's solution for the estimation of glucose or invert sugar depends on the power which glucose possesses (in common with many simple aldoses and ketoses) of reducing quantitatively, alkaline copper salts with the separation of cuprous oxide. The reducing power of glucose is made use of in silvering mirrors where the metallic silver obtained by reducing ammoniacal solutions of silver salts is deposited on the glass in the form of a highly reflecting film; another use of glucose reduction on an industrial scale is the boiling of indigo with glucose and alkali to form the soluble indigo-white which forms the basis of the 'vat'.

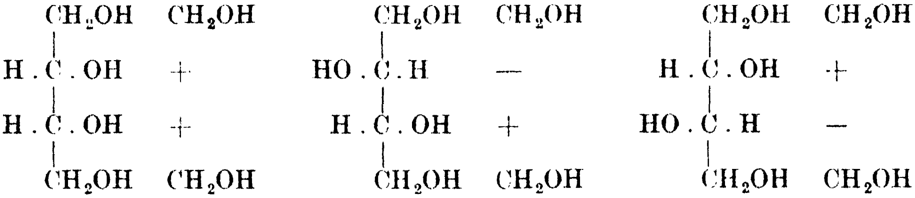
The Sugar-alcohols

When simple sugars are themselves reduced, a group of polyhydric alcohols results; many references have been made in previous pages to members of this group, and it is proposed to deal more fully with the family at this point.

Every monosaccharide sugar, when reduced, yields a polyhydric alcohol, and it was through these alcohols that much was learnt of the sugar structures, more especially since most of the alcohols are also to be obtained in alternative ways, and since some of them occur naturally. In Table IV are shown the principal members of the polyhydric sugar families and their physical properties; more details of their chemistry are given below.

THE ERYTHRITOLS

First prepared by Stenhouse[1] in 1848, from the orchella lichens, and the formula elucidated by Strecker,[2] *i*-erythritol, is the most common of this family.



$$\begin{array}{ll} & CH_2OH \quad CH_2OH \\ & \;| \\ H\,.\,C\,.\,OH & \quad + \\ & \;| \\ H\,.\,C\,.\,OH & \quad + \\ & \;| \\ & CH_2OH \quad CH_2OH \end{array} \qquad \begin{array}{ll} & CH_2OH \quad CH_2OH \\ & \;| \\ HO\,.\,C\,.\,H & \quad - \\ & \;| \\ H\,.\,C\,.\,OH & \quad + \\ & \;| \\ & CH_2OH \quad CH_2OH \end{array} \qquad \begin{array}{ll} & CH_2OH \quad CH_2OH \\ & \;| \\ H\,.\,C\,.\,OH & \quad + \\ & \;| \\ HO\,.\,C\,.\,H & \quad - \\ & \;| \\ & CH_2OH \quad CH_2OH \end{array}$$

i-Erythritol (116) D-Erythritol * (117) L-Erythritol *

It will be observed that erythritol has two asymmetric carbon atoms, and should, like tartaric acid which has a similar type of asymmetry, exist in one inactive and two active forms. These are depicted in the formulæ (116) and (117). They are all known, and have been synthesised. When butadiene (118) is allowed to react with a molecule of bromine some 1, 4- addition takes place, and 1, 4-dibrombutene-2 (119) is formed. This, on treatment with silver acetate

TABLE IV

No. of C atoms	Name	Occurrence	Configuration of core	M.P.	$[\alpha]_D$
4	*i*-Erythritol	Lichens, algæ	+ +	126° (b. 329°)	Inactive
4	D-Erythritol	Synthesis	— +	89°	— 4·4° (water)
4	L-Erythritol	Synthesis	+ —	89° (*dl*, 72°)	
5	D-Arabitol	Lichens	+ — —	103°	Very small
5	L-Arabitol	Synthesis	— + +	103	
5	Adonitol	*Adonis vernalis*	+ + +	102°	Inactive
5	Xylitol	Synthesis	+ — +		Inactive
5	Pentaerythritol	$C(CH_2OH)_4$	—	260°	Inactive
6	L-Methylpentitol-(rhamnitol)	Synthesis	— — + +		
6	Dulcitol	Madagascar manna	+ — — +	188°	Inactive
6	D-Mannitol	Manna, normal urine	+ + — —	166°	— 0·25° (water)
6	L-Mannitol	—	— — + +		
6	D-Sorbitol	Mountain ash berries	+ + — +	111°	— 1·73° (water)
6	L-Sorbitol		— — + —		
6	D-Iditol	Mountain ash berries	+ — + —	73°	— 3·5° (water)
6	L-Iditol		— + — +		
6	D-Talitol	Redn. of talose	+ — — —		
†6	L-Talitol		— + + +		
7	Persitol	*Laurus persca*	+ + — — —		Dextro rotatory in borax soln.
7	Volemitol	Primulas and moulds	?	155°	+ 2·65°

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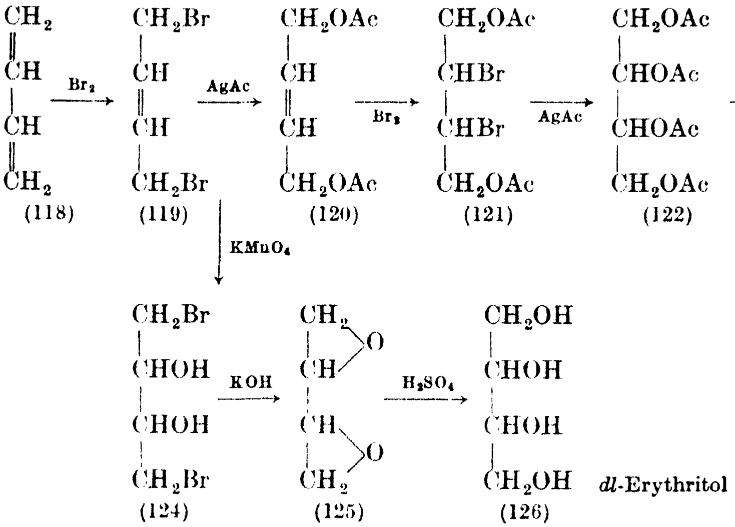
[1] Stenhouse, *Phil. Trans.*, 1848, 76 ; 1849, 399.

[2] Strecker, *Ann. Chim. Phys.*, 1852, [3] **35**, 138.

* See p. 795 for anomalous nomenclature of D- and L-erythritols.

† An additional hexitol from allose, CH_2OH + + + + CH_2OH is possible, but is virtually unknown.

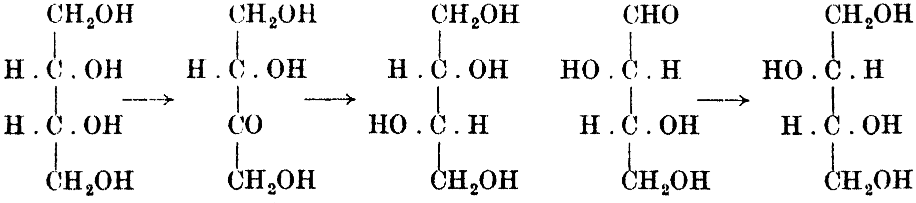
yields the diacetylbuten-2-diol-1, 4 (120) which, in turn, is capable of adding a further molecule of bromine, giving the 2, 3-dibromo compound (121). A second treatment with silver acetate converts the bromo- compound to the tetra-acetate of *i*-erythritol (122), from which the L-erythritol (123) itself can be obtained by hydrolysis. If, however, 1, 4-dibromobutene-2 is oxidised with permanganate it yields a glycol (124). This on digestion with potassium hydroxide is converted to the compound 1, 2 : 3, 4-di-epoxybutane (125) which is hydrolysed by dilute sulphuric acid to a racemic mixture of D- and L-erythritol (126). To avoid



$$\begin{array}{c}CH_2\\ \|\\ CH\\ |\\ CH\\ \|\\ CH_2\\ (118)\end{array} \xrightarrow{Br_2} \begin{array}{c}CH_2Br\\ |\\ CH\\ \|\\ CH\\ |\\ CH_2Br\\ (119)\end{array} \xrightarrow{AgAc} \begin{array}{c}CH_2OAc\\ |\\ CH\\ \|\\ CH\\ |\\ CH_2OAc\\ (120)\end{array} \xrightarrow{Br_2} \begin{array}{c}CH_2OAc\\ |\\ CHBr\\ |\\ CHBr\\ |\\ CH_2OAc\\ (121)\end{array} \xrightarrow{AgAc} \begin{array}{c}CH_2OAc\\ |\\ CHOAc\\ |\\ CHOAc\\ |\\ CH_2OAc\\ (122)\end{array} \xrightarrow{H_2SO_4} \begin{array}{c}CH_2OH\\ |\\ CHOH\\ |\\ CHOH\\ |\\ CH_2OH\\ (123)\\ i\text{-Erythritol}\end{array}$$

$$(119) \xrightarrow{KMnO_4} \begin{array}{c}CH_2Br\\ |\\ CHOH\\ |\\ CHOH\\ |\\ CH_2Br\\ (124)\end{array} \xrightarrow{KOH} \begin{array}{l}CH_2\\ |\;\rangle O\\ CH\\ |\\ CH\\ |\;\rangle O\\ CH_2\\ (125)\end{array} \xrightarrow{H_2SO_4} \begin{array}{c}CH_2OH\\ |\\ CHOH\\ |\\ CHOH\\ |\\ CH_2OH\\ (126)\end{array} \; dl\text{-Erythritol}$$

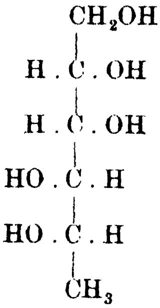
the difficult separation of this racemic mixture into D- and L- components, they can be prepared by alternative methods ; D-erythritol may be obtained from the internally compensated *i*-erythritol (127) by the action of the sorbose bacteria which oxidises it to an active erythrulose (128) (presumably destroying its antimer). When the erythrulose is reduced by sodium amalgam D-erythritol is obtained (129).



$$\begin{array}{c}CH_2OH\\ |\\ H.C.OH\\ |\\ H.C.OH\\ |\\ CH_2OH\\ (127)\end{array} \longrightarrow \begin{array}{c}CH_2OH\\ |\\ H.C.OH\\ |\\ CO\\ |\\ CH_2OH\\ (128)\end{array} \longrightarrow \begin{array}{c}CH_2OH\\ |\\ H.C.OH\\ |\\ HO.C.H\\ |\\ CH_2OH\\ (129)\end{array} \qquad \begin{array}{c}CHO\\ |\\ HO.C.H\\ |\\ H.C.OH\\ |\\ CH_2OH\\ (130)\end{array} \longrightarrow \begin{array}{c}CH_2OH\\ |\\ HO.C.H\\ |\\ H.C.OH\\ |\\ CH_2OH\\ (131)\end{array}$$

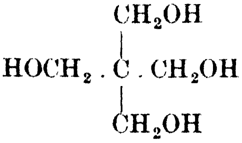
L-Erythritol is obtained by the reduction of D-threose (130-131). It will have been observed that the D- and L- nomenclature of the erythritols is anomalous, and has not followed the rule that D- compounds must have the H— C— OH configuration on the penultimate carbon ; to remedy this it has been suggested that L-erythritol should be called D-threitol, and D-erythritol, L-threitol. The suggestion is a good one, and might with advantage be adopted.

Of the pentitols, adonitol is most commonly met with, being the naturally occurring alcohol of *Adonis vernalis*. It can be obtained by the reduction of D- or L-ribose, just as the arabitols and xylitol are formed from arabinose and xylose by reduction ; they present no unusual features. Two unusual members of this series are rhamnitol (132) from the reduction of rhamnose and pentaerythritol (133) a symmetrical tetrahydroxy*neo*pentane. The latter is a synthetic



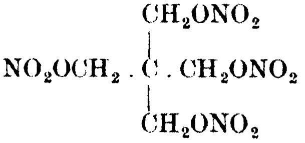
$$\begin{array}{c} CH_2OH \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ HO.C.H \\ | \\ HO.C.H \\ | \\ CH_3 \end{array}$$

(132)



$$\begin{array}{c} CH_2OH \\ | \\ HOCH_2.C.CH_2OH \\ | \\ CH_2OH \end{array}$$

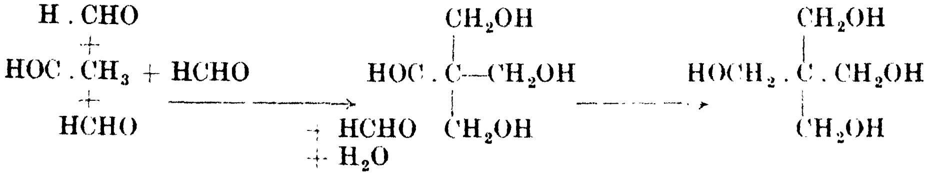
(133)



$$\begin{array}{c} CH_2ONO_2 \\ | \\ NO_2OCH_2.C.CH_2ONO_2 \\ | \\ CH_2ONO_2 \end{array}$$

(134)

substance obtained by the reaction of a molecule of acetaldehyde with four of formaldehyde in the presence of lime :—



$$\begin{array}{c} H.CHO \\ + \\ HOC.CH_3 + HCHO \\ + \\ HCHO \end{array} \longrightarrow \begin{array}{c} CH_2OH \\ | \\ HOC.C—CH_2OH \\ | \\ CH_2OH \end{array} \begin{array}{l} \\ \\ \\ \\ + HCHO \\ + H_2O \end{array} \longrightarrow \begin{array}{c} CH_2OH \\ | \\ HOCH_2.C.CH_2OH \\ | \\ CH_2OH \end{array}$$

It is a crystalline substance, the tetranitrate of which (134) is produced in large quantities as an industrial explosive.

HEXITOLS

Proust[1] discovered mannite in 1806 in the so-called 'manna' which is the solidified sap of varieties of ash (*Fraxinus ornus* and *Fraxinus rotundifolia*), found in S. Europe, especially Calabria and Sicily. (The manna of the Israelites in the wilderness was an exudation of a similar character from *Tamarix mannifera* but contains no mannite). It can be obtained readily by the reduction of D-mannose or D-fructose, the latter of which is easily obtainable industrially. D-Mannite is found in most fungi, in normal urine and a vast variety of vegetable organisms. When Madagascar manna is extracted with water it gives a good yield of D-dulcitol, a fact noted by Hünefeld in 1836,[2] whilst Laurent[3] in 1851, recognised that the new substance was an isomer of mannitol. D-Sorbitol and *d*-iditol are found in the berries of mountain ash, but sorbitol is produced in large quantities on an industrial scale by the electrolytic reduction of glucose, and may now be bought by the ton, either as the pure substance or as a thick syrupy aqueous solution. The latter has many of the properties of glycerol, and has been used to replace it in pharmaceutical preparations, and other cases where the physical nature of the sorbitol or glycerol is more important than its chemical structure. The term 'humectant' is used to signify a substance of this type.

These hexitols are of value to the bacteriologist, since their fermentation (or otherwise) by various species of typhoid and dysentery organisms is used as a means of identification of the species.

The chemistry of the hexitols does not call for a detailed survey; in general the six hydroxyl groups can be esterified to give hexa- derivatives, such as the hexa-acetate and hexanitrate. Vigorous reduction by hydriodic acid gives iodohexane, and mild oxidation leads to the hexose sugars. Brigl[1] has studied the oxide rings which can be induced in mannitol; these include a

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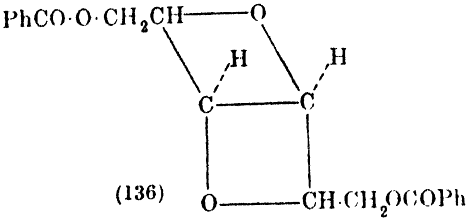
[1] Proust, *Ann. Chim.*, 1806, **67**, 143.

[2] Hünefeld, *J. Pr. Chem.*, 1836, **7**, 233.

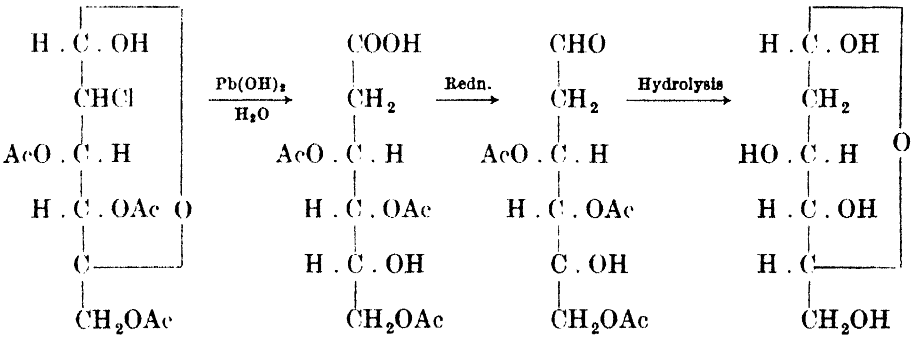
[3] Laurent and Gerhardt, *C.R.*, 1851, **32**, 29.


(136)

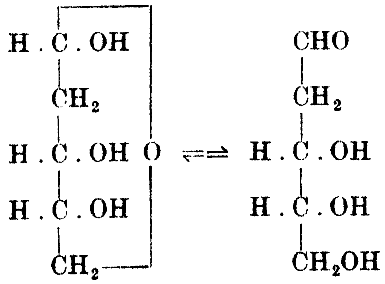
di-furanose structure from 1, 6-dibenzoyl-D-mannitol, which is quite stable, and is probably best represented by the *cis* structure (136); it will be noted that the epoxy- groups are in the 2, 4 and 3, 5 positions.

THE DESOXY SUGARS

The reduction of ordinary aldohexoses to their corresponding sugar-alcohols does not exhaust the possibilities of reduction, although in some cases a roundabout method must be used to obtain desoxy- sugars. The term 'desoxy' is usually restricted to those compounds in which a single group has been deprived of its oxygen atom as in 2-desoxyglucose (140), which may be obtained from triacetyl-2-chloroglucose (137) on treatment with an aqueous suspension of lead hydroxide, giving the triacetyldesoxygluconic acid (138) which can be reduced to triacetyl-2-desoxyglucose (139) and finally hydrolysed to 2-desoxyglucose. Mention has already been made of some desoxy-sugars (p. 789); a fuller description of them is given below.



(137) (138) (139) (140)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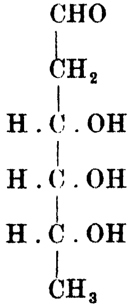
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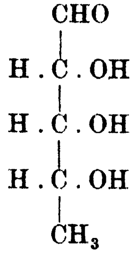
(143)

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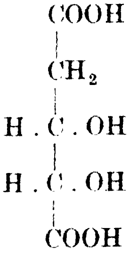
[1] Brigl and Grüner, *Ber.*, 1933, **66B**, 1945.

The simplest 2-desoxy- sugar of importance is 2-desoxy-D-ribose (141); inspection of the formula will show that since the 2-carbon atom has lost its asymmetry this sugar could equally well have been named 2-desoxy-D-arabinose. The interest of this sugar lies in its isolation[1] from the nucleic acid of the thymus gland. Other desoxy- sugars owe their interest to their occurrence in natural substances, digitoxose (142), for example, being discovered in digitoxin by Kiliani[2] nearly half a century ago. He established the empirical formula of digitoxose as $C_6H_{12}O_4$, and observed that although it was a sugar, it was not a 'carbohydrate' in the strict sense of the term, being deficient in two atoms of oxygen. Since it gave a phenylhydrazone and no osazone Kiliani formed the opinion that the second carbon atom was reduced, and since acetic acid is formed during its oxidation[3] a methyl group must exist in the structure, which can only be at the '6' carbon. This established digitoxose as a 2, 6-desoxy-sugar.

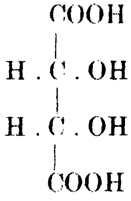
The final elucidation of the structure of digitoxose depends on two main points:—

(1) The isolation of 1, 2-dihydroxyglutaric acid (144) and mesotartaric acids (145) on oxidation of digitoxose with nitric acid which proves that the '3' and '4'- carbon atoms of the sugar are *cis*-, and



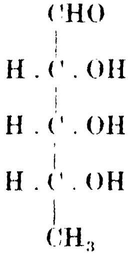
$$\begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ COOH \end{array}$$

(144)



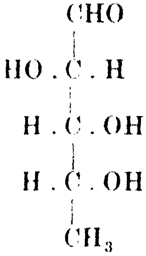
$$\begin{array}{c} COOH \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ COOH \end{array}$$

(145)



$$\begin{array}{c} CHO \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ CH_3 \end{array}$$

(146)



$$\begin{array}{c} CHO \\ | \\ HO.C.H \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ CH_3 \end{array}$$

(147)

(2) the conversion[4] of digitoxose through an intermediate stage to the methyl tetrose (146) which, although not identical with D-arabomethylose (147), has the same osazone. The structure of the methyltetrose from digitoxose must, therefore, be (146), in which the three active groups are all *cis*-, or D- groups. This confirms the structure (142) for digitoxose. Cymarose is a monomethylether of digitoxose, giving that sugar on demethylation. The position of the methoxy group on carbon atom '3' was elucidated by Elderfield in 1935.[5]

THE OXIDATION OF SUGARS

Direct oxidation of sugars usually affects the terminal groups; the following types of compound are all potentially capable of being formed; the original aldose (148) is frequently oxidised to the glycuronic acid (151); to the glyconic acid (150) or the dicarboxylic acid (152); the dialdehyde form (149) is seldom encountered.

If the oxidation takes place in a ketose, or if an indirect method is used for oxidation, groups other than the terminal ones may be affected. The osones or 2-keto- sugars (153) are examples; Kiliani investigated a 5-keto-sugar (154) and its ketogluconic acid (155).

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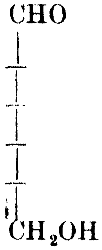
[1] Levene and Loudon, *J. Biol. Chem.*, 1928, **81**, 711; 1929, **83**, 793.
[2] Kiliani, *Arch. Pharm.*, 1895, **233**, 319; 1896, **234**, 486.
[3] Kiliani, *Ber.*, 1899, **32**, 2196; see also *ibid.*, 1905, **38**, 4040.
[4] Cloetta, *Arch. exptl. Path. u. Pharm.*, 1920, **88**, 113. Micheel, *Ber.*, 1930, **63**, 347.
[5] Elderfield, *J. Biol. Chem.*, 1935, **111**, 527.



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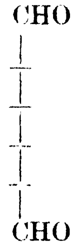

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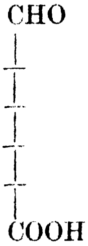

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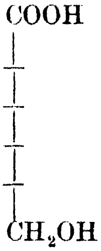

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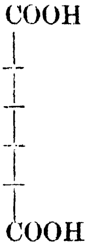
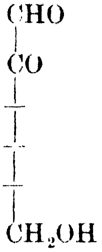


(152)

Strictly speaking, ascorbic acid is an 'oxidised' sugar, but consideration of its structure is deferred to Chapter XI. Some interest centres round the two



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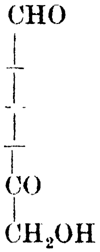

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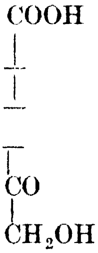
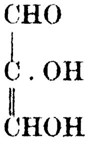


(155)

substances reductone (156) and reductic acid (157), both of which have a strong chemical likeness to ascorbic acid, and may be intermediates in sugar metabolism.



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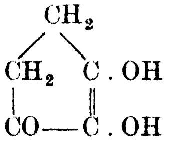

(157)

The glycuronic acids are of paramount importance in biological studies; they occur as polymerides in algins and pectins; as conjugated compounds in the glucoproteins and in urine. They are part of the detoxication mechanism of animals and slowly excreted substances are, where possible, removed from the animal system by combination with a glycuronic acid giving a compound which as a rule is excreted readily. This was detected by Schmiedeberg,[1] over sixty years ago, who, on feeding camphor to dogs, recovered a bornyl glycuronate. There are several common glycuronic acids, D-glucuronic acid, D-galacturonic acid and D-mannuronic acid, whilst others such as D-alluronic acid are known.

D-Glucuronic acid (158) is a substance utilised by the body in detoxication; the substance to be detoxicated forms a compound analogous to a glycoside, in this case, a glycuronide. Levene has shown that D-glucuronic acid is a constituent unit of the mucoproteins, and it is probable that the free acid required in detoxication processes *in vivo*, is obtained by the breakdown of mucin.

D-Glucuronic acid itself is an intractable syrup, but its lactone (159) is readily crystallisable and has been synthesised by several methods, e.g., Zervas and

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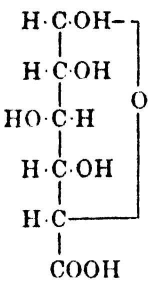
[1] Schmiedeberg and Meyer, *Z. Physiol. Chem.*, 1879, **3**, 422.

Sessler[1] obtained the essential intermediate 1, 2-acetone-3, 5-benzylidene D-glucofuranose (160); this contains a free hydroxyl on the terminal carbon atom and may be oxidised to the corresponding acid from which the benzylidene group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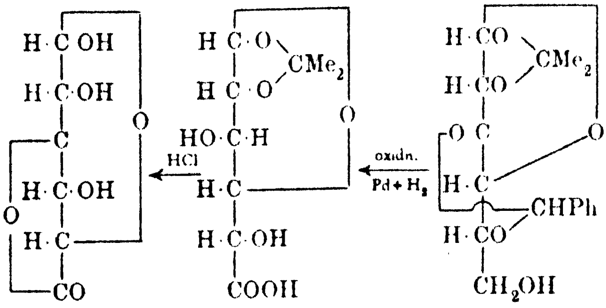
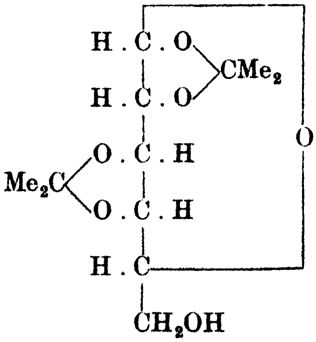


(159) (160)

can be removed by catalytic reduction with palladium and hydrogen leaving a 1, 2-acetone derivative of D-glucuronic acid with a furanose ring. Hydrolysis with dilute hydrochloric acid converts the acetone derivative to D-glucuronic alctone (159).

Gums and the mucilages of plants are mainly polysaccharides of D-glucuronic and *d*-galacturonic acids. The latter forms a particularly high percentage of purified citrus pectin from which it is easily prepared.[2] D-Galacturonic acid is much easier to handle than is D-glucuronic acid, being readily crystallisable. It was easily synthesised from 1, 2, 3, 4-diacetone galactopyranose (161) which has the necessary free terminal group. Oxidation to the corresponding diacetone-acid (162) and hydrolysis yield the crystalline galacturonic acid (163). As with the simple sugars, two methylgalacturonides exist, and there is some evidence for a pyranose-, rather than a furanose-ring. D-Mannuronic acid is obtained by the hydrolysis of the algins[3] of seaweed; its lactone has been obtained by reduction of D-mannosaccharic lactone.[4]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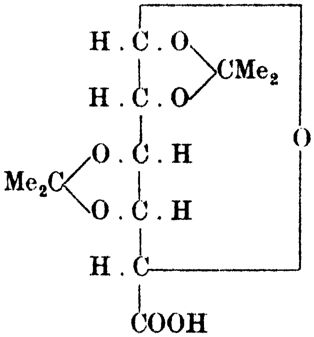
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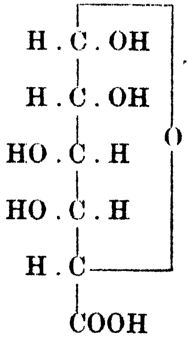
(163)

The Glyconic Acids.—Only two of the glyconic acids—D-galactonic and D-talonic acids are easily obtainable in crystalline form, the others usually being met with as syrups. They form crystalline lactones, which are presumably analogous to the glycuronic lactones. Glyconic acids are important in sugar chemistry, since they are intermediates in the passage from pentose to hexose sugars; thus if an aldose (164) is allowed to react with hydrogen cyanide the nitrile of the glyconic acid is formed (165) and the acid itself may be formed

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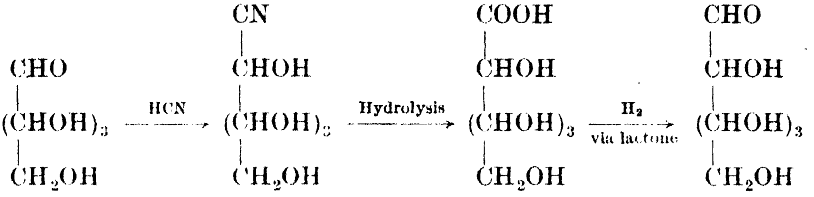
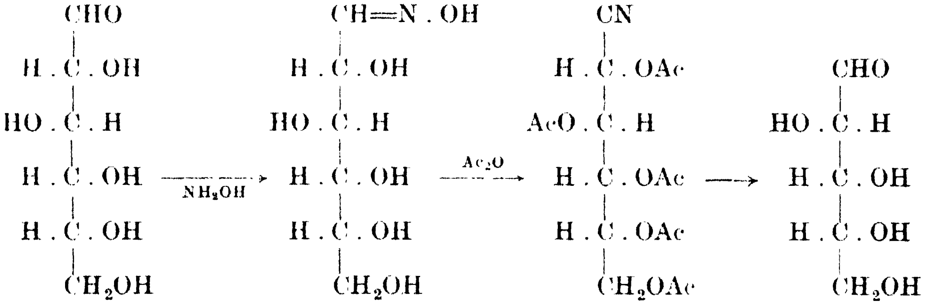
[1] Zervas and Sessler, *Ber.*, 1933, **66**, 1326.
[2] Link, *J. Biol. Chem.*, 1933, **100**, 385.
[3] Nelson and Cretcher, *J.A.C.S.*, 1930, **52**, 2130.
[4] Niemann and Link, *J. Biol. Chem.*, 1933, **100**, 407.



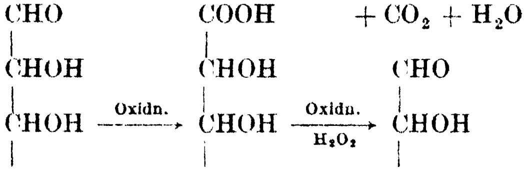
(164) (165) (166) (167)

by hydrolysis (166); reduction of the lactone to the aldohexose (167) follows. This procedure, which often goes by the name of 'Kiliani's reaction', has been used to build up aldoses with up to nine and ten atoms. The reverse process can be carried out by heating the oxime of an aldose (e.g., that of D-glucose (168)) with



(168) (169) (170) (171)

acetic acid when the acetyl derivative of D-gluconic nitrile is formed (169-170). Ammoniacal silver nitrate converts this to the aldose (171), hydrolysing the acetyl groups and removing the elements of HCN. In this way D-arabinose is obtained from D-glucose. The glyconic acids also play an intermediate part in Ruff's degradation, wherein the aldohexose is converted to the glyconic acid, the calcium salt of which is oxidised by hydrogen peroxide in the presence of a trace of ferric iron to the next lower aldose:—



Of the glyconic acids, D-gluconic acid is best known, as it is prepared in industrial quantities by the oxidation of aerated solutions of glucose by a micro-organism,[1] *B. gluconicum*. The fermentation can be carried out in the presence of chalk and the D-gluconic acid isolated as the calcium salt. Calcium gluconate solution is used as an injectable calcium preparation in medicine and the borogluconate is widely used in veterinary medicine. The glyconic acids from other sugars are known, but offer no outstanding features of interest, excepting their epimerisation which is a valuable weapon in probing sugar structures. If a glyconic acid (e.g., D-gluconic acid) is heated in quinoline solution there separates on cooling a mixture of the original D-gluconic acid

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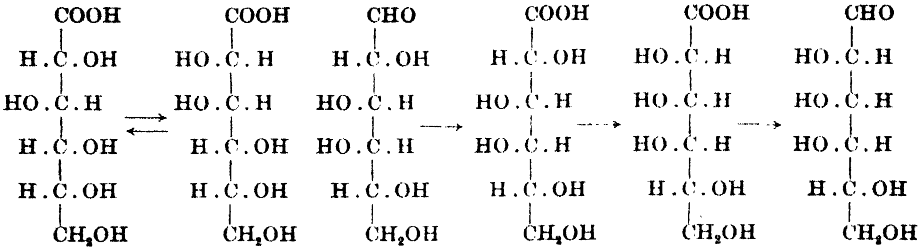
[1] Hermann and Neuschul, *Biochem. Z.*, 1936, **287**, 400.

(172) and D-mannonic acid (173), epimerisation having taken place at the '2' carbon atom. The effect of this is that any sugar can be converted to its epimer *via* the glyconic acid, e.g., D-galactose (174) can be converted to D-talose (177) *via* the glyconic acids, D-galactonic acid and D-talonic acid (175) and (176).



(172) (173) (174) (175) (176) (177)

The Saccharic Acids.—Scheele coined the name 'saccharic acid' to describe the acid obtained by oxidising cane sugar with nitric acid; his new acid consisted of a mixture, largely oxalic acid but with a second acid which Hess[1] correctly characterised in 1837, and to which he gave the original name. In the same way Scheele obtained mucic acid from lactose by nitric oxidation. Later investigators showed that all aldohexoses yield a dicarboxylic acid on oxidation, the optical activity or internal compensation of which throws considerable light on the structure of the hexoses themselves. The various acids and the sugars from which they are obtained are set out in Table V. It will be noted that there are ten saccharic acids, two of which are inactive and the remainder divided into four pairs of D- and L-enantiomorphs.

TABLE V

Sugars	Dicarboxylic acids	Configuration	Properties
D-Allose L-Allose	Allomucic acid	+ + + +	m. 199° Inactive
D-Altrose D-Talose	D-Talomucic acid	+ + + —	m. 158°
L-Altrose L-Talose	L-Talomucic acid	— — — +	m. 158°
D-Glucose L-Gulose	D-Saccharic acid	+ + — +	m. 125–126° Lactone, m. 130–132°
L-Glucose D-Gulose	L-Saccharic acid	— — + —	m. 125°
D-Mannose	D-Mannosaccharic acid	+ + — —	Lactone, m. 180–190°
L-Mannose	L-Mannosaccharic acid	— — + +	—
D-Galactose L-Galactose	Mucic acid	+ — — +	m. 215° Inactive
D-Idose	D-Idosaccharic acid	+ — + —	—
L-Idose	L-Idosaccharic acid	— + — +	—

These correspond exactly with the ten hexitols (p. 794).

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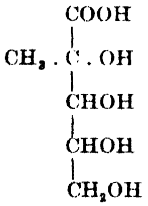
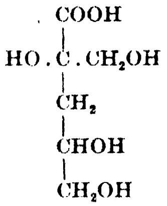
[1] **Hess, *Ann. Pharm.*, 1837, 26, 1.**

Saccharinic Acids.—It will have been noted that all discussions of epimerisation and the like have centred round the glyconic and saccharic acids. This is not because the sugars themselves do not undergo changes when submitted to similar reagents, but because such changes are so deep-seated and far-reaching that little can be gathered from their study unless the constitution of the sugar itself is already completely known. Thus, when alkalies are allowed to react upon *d*-glucose, disaccharides make their appearance in solution, together with a group of acids called saccharinic acids. The main types of saccharinic acids



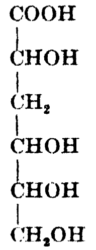
$$\begin{array}{l} \quad\;\; COOH \\ \qquad | \\ CH_3.C.OH \\ \qquad | \\ \quad\;\; CHOH \\ \qquad | \\ \quad\;\; CHOH \\ \qquad | \\ \quad\;\; CH_2OH \end{array}$$

3-Asymmetric atoms
8 Forms
SACCHARINIC
(178)



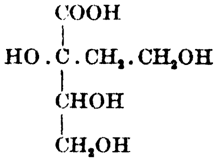
$$\begin{array}{l} \quad\;\; COOH \\ \qquad | \\ HO.C.CH_2OH \\ \qquad | \\ \quad\;\; CH_2 \\ \qquad | \\ \quad\;\; CHOH \\ \qquad | \\ \quad\;\; CH_2OH \end{array}$$

2-Asymmetric atoms
4 Forms
iso-SACCHARINIC
(179)



$$\begin{array}{l} COOH \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

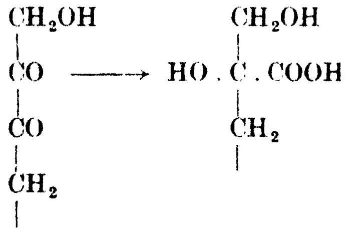
3-Asymmetric atoms
8 Forms
meta-SACCHARINIC
(180)



$$\begin{array}{l} \quad\;\; COOH \\ \qquad | \\ HO.C.CH_2.CH_2OH \\ \qquad | \\ \quad\;\; CHOH \\ \qquad | \\ \quad\;\; CH_2OH \end{array}$$

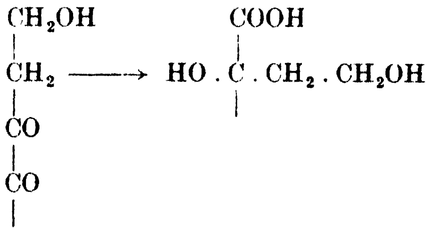
2-Asymmetric atoms
4 Forms
para-SACCHARINIC
(181)

are set out in formulæ (178) to (181), but the mechanism of their formation is not properly understood. Various explanations given by Nef,[1] and by Benoy and Evans [2] depend on the formation of an αα-diketone, followed by a benzilic acid rearrangement, as shown in formulæ (182) to (185).



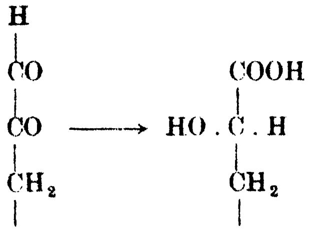
$$\begin{array}{l} CH_2OH \\ | \\ CO \\ | \\ CO \\ | \\ CH_2 \\ | \end{array} \xrightarrow{\qquad} \begin{array}{l} \quad\;\; CH_2OH \\ \qquad | \\ HO.C.COOH \\ \qquad | \\ \quad\;\; CH_2 \\ \qquad | \end{array}$$

(182)
iso-SACCHARINIC



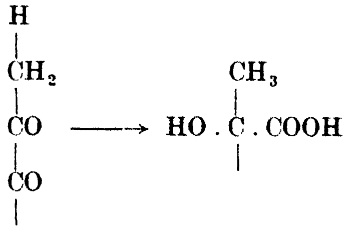
$$\begin{array}{l} CH_2OH \\ | \\ CH_2 \\ | \\ CO \\ | \\ CO \\ | \end{array} \xrightarrow{\qquad} \begin{array}{l} \quad\;\; COOH \\ \qquad | \\ HO.C.CH_2.CH_2OH \\ \qquad | \end{array}$$

(183)
para-SACCHARINIC



$$\begin{array}{l} H \\ | \\ CO \\ | \\ CO \\ | \\ CH_2 \\ | \end{array} \xrightarrow{\qquad} \begin{array}{l} \quad\;\; COOH \\ \qquad | \\ HO.C.H \\ \qquad | \\ \quad\;\; CH_2 \\ \qquad | \end{array}$$

(184)
meta-SACCHARINIC



$$\begin{array}{l} H \\ | \\ CH_2 \\ | \\ CO \\ | \\ CO \\ | \end{array} \xrightarrow{\qquad} \begin{array}{l} \quad\;\; CH_3 \\ \qquad | \\ HO.C.COOH \\ \qquad | \end{array}$$

(185)
SACCHARINIC

It will be observed that the mechanism suggested for the formation of these four acids is a regular benzilic acid transformation from αα-diketo sugars all containing the —CO . CO . CH_2— chain; the first group (182-183) of carbon atoms at '2', '3' and '4'; the second group (184-185) at '1', '2' and '3'. Benoy and Evans postulate the formation of the intermediate substances through an enediol form which is shown in the formulæ below :—

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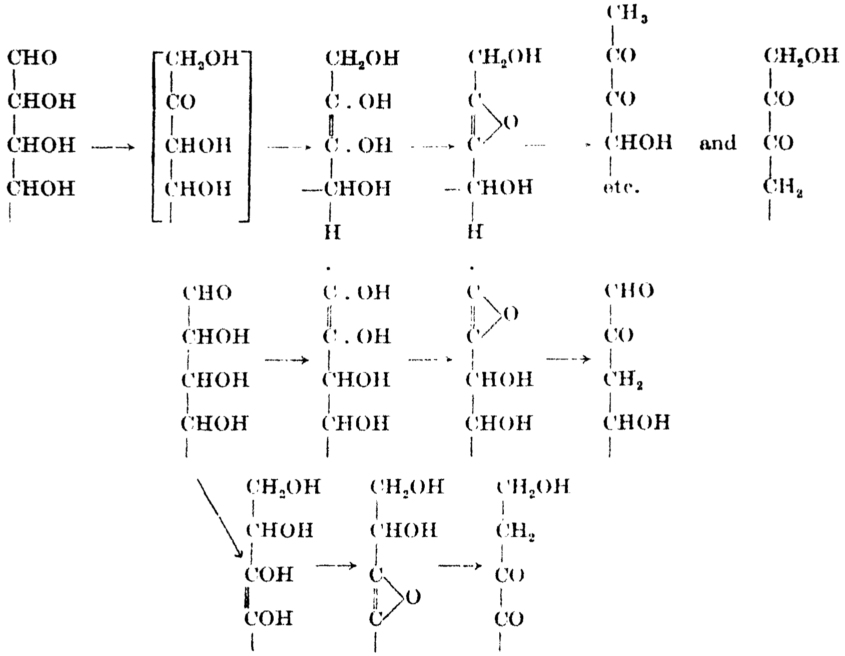
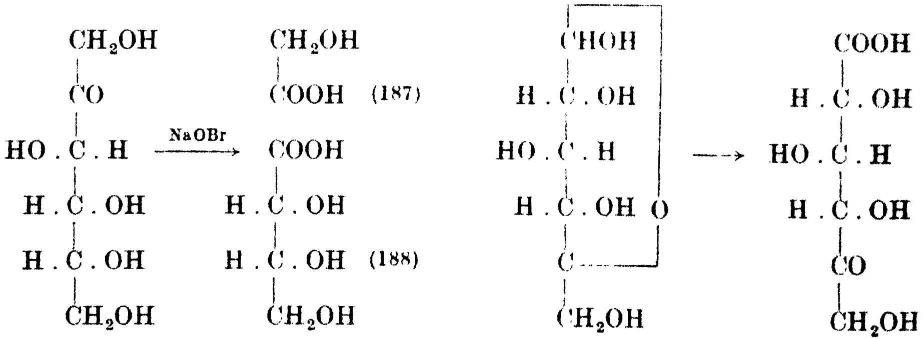
[1] Nef., *Ann.*, 1914, **403**, 206.
[2] Benoy and Evans, *J.A.C.S.*, 1926, **48**, 2675.



The formulæ of the various saccharinic acids which can be developed from the four varieties just described (182 to 185) indicate the potential existence of twenty-four isomers ; very few of these are known.

Many other oxidation products of simple sugars can be obtained and in the processes described above for obtaining glyconic, saccharic and saccharinic acids it must not be thought that the substances referred to are the sole products ;

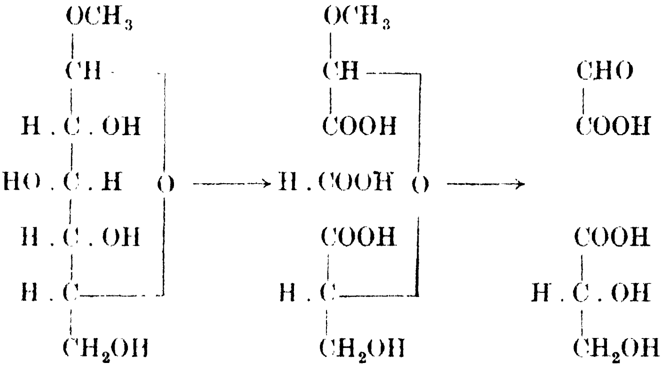


(186) (187) (188) (189) (190)

they are often accompanied by numerous other products, the genesis of which is difficult to elucidate. This is due, in large measure, to the labile nature of the aldose structure ; even cold saturated lime water will induce deep-seated changes in D-glucose, and both D-mannose and D-fructose have been isolated from such a solution and it is known that many other substances are present. Since nearly all oxidising agents are acid or alkaline in reaction, the formation of numerous by-products is inevitable.

Thus, the reaction of sugars with hypobromites has yielded a wide variety of products. Under vigorous conditions ketoses are attacked between the second and third carbon, D-fructose (186) gives glycollic acid (187) and D-erythronic acid (1, 2, 3-trihydroxybutane acid-4) (188), a fact which gives an additional cross-check on the structures already arrived at for these compounds.

Again, barium hypobromite oxidises D-glucose (189)[1] to 5-ketogluconic acid in good yield, thus making this keto-acid available in quantity (190). This oxidation must take place either with the open chain form of D-glucose, or by attack at the pyran ring; when methyl glycosides (191) are oxidised with hypobromite[2] the pyran structure remains intact, oxidation opening the ring between the second and third carbon atom, leading to the mixed acetal (192) which can be opened by hydrolysis to glyoxalic acid and glyceric acid (193). An initial oxidation with periodic acid followed by hypobromite oxidation increases the yield of the acetal (192) to 60-70 per cent. Pyranose sugars show formic acid formation from the central carbon atom during such oxidations; furanose structures give no formic acid.



(191) (192) (193)

Finally, the ability of sugars, such as glucose, fructose and other aldo sugars, to be oxidised in alkaline solution has led to extensive application of the 'copper reducing power' to the estimation of these bodies, since the amount of cuprous oxide obtained from a given weight of aldose in reaction with an alkaline copper solution is constant under controlled conditions. Fehling's solution has, for generations, served as the basis of a number of practical methods of sugar analysis, and has been modified to give consistent results under a variety of circumstances.

THE DEHYDRATION OF SUGARS

The simple loss of one molecule of water from D-glucose leads to a product, $C_6H_{10}O_5$, to which the name 'glucosan' was originally given. An enquiry into the mechanism of this loss of water and the structure of the remaining product led to the recognition of a number of isomeric glucosans, for it appears that glucose can lose one molecule of water in almost every conceivable way. For convenience, the products are now divided into two groups (*a*) the glucoseen group, where dehydration has led to a double bond and (*b*) the anhydroglucose group, comprising 1, 2-, 1, 3-, 1, 4-, 1, 5-, and 1, 6-, anhydro forms, the oxide ring being situated as indicated by the figures; this ring is, of course, independent of any normal pyranose or furanose configuration which may also be present. The formulæ (194 to 199) show 1, 2- and 5, 6-glucoseen, and also some of the anhydroglucoses.

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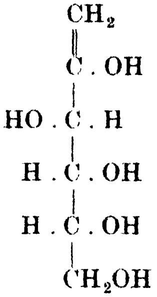
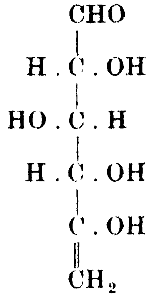
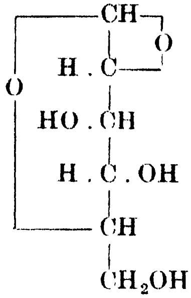
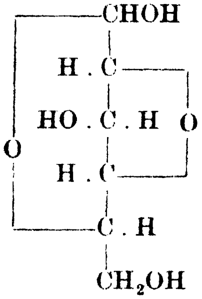
[1] Reichstein and Neracher, *Helv. Chim. Acta*, 1935, **18**, 892.

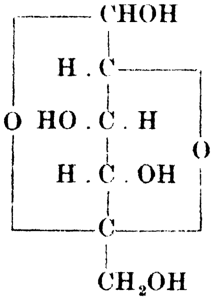
[2] Jackson and Hudson, *J.A.C.S.*, 1936, **58**, 378.

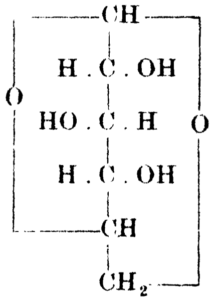

1, 2-Glucoseen
(194)


5, 6-Glucoseen
(195)

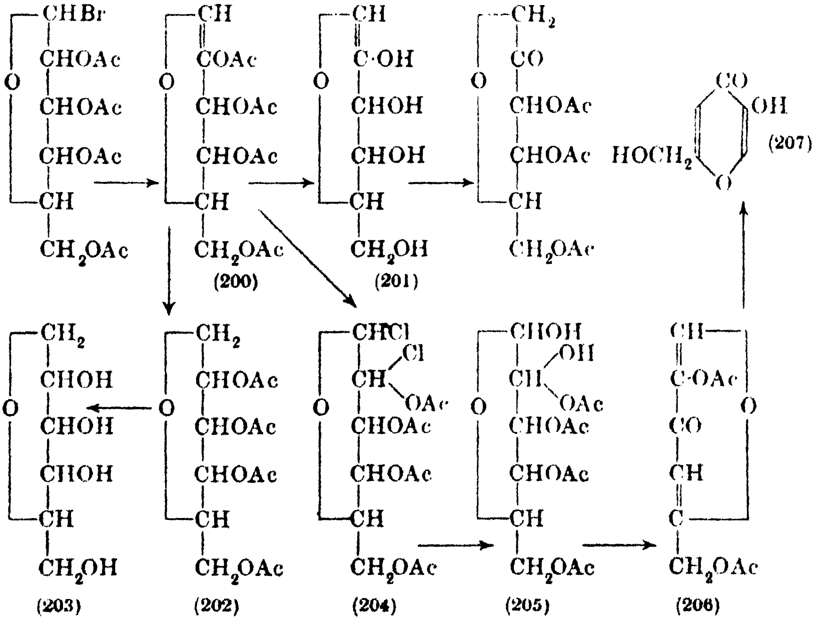

1, 2-Anhydroglucose
(196)


2, 4-Anhydroglucose
(197)


2, 5-Anhydroglucose
(198)


1, 6-Anhydroglucose
(199)

The 1, 2- glucoseens are perhaps the best known of this group, being obtained by the action of bases such as diethylamine on acetobromoglucose,[1] the effect being to remove hydrogen bromide, leaving a 1, 2-glucoseen tetra-acetate (200).



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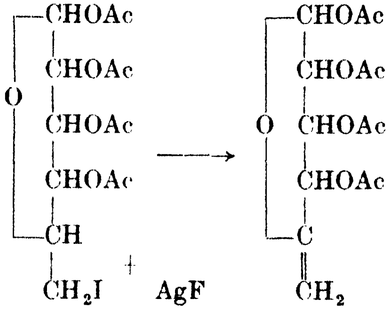
[1] Maurer and Mahn, *Ber.*, 1927, **60**, 1316.

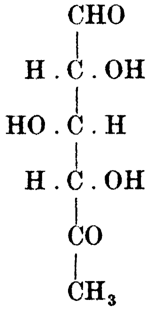
When this tetra-acetyl derivative is hydrolysed, the enol of fructose (201) should be produced, but fructose has never been isolated by this method, although if the acetyl derivative (200) is reduced at the double bond by palladium and hydrogen to the dihydro- derivative (202) the latter can be deacetylated to styracitol (203).[1]

One of the most important conversions of this series is that which takes place when tetra-acetylglucoseen (200) reacts with chlorine, forming the dichloro-addition product (204) which can be decomposed by silver hydroxide to the substance (205), a dihydrate of glucosone tetra-acetate. This substance, on boiling with a solution of acetic anhydride in pyridine, is converted to diacetylkojic acid (206) which, in turn, may be deacetylated to kojic acid itself (207). This acid is one of the principal metabolites of the moulds, and can be obtained in quantity by the fermentation of glucose by *Aspergillus flavus*,[2] and its formation by the changes shown above is an important link between chemical and biochemical processes.

The 5, 6-glucoseens are obtained by reacting 6-iodotetra-acetylglucose (208) with silver fluoride (209). The structure of a 5, 6-glucoseen can only be retained



(208) (209)

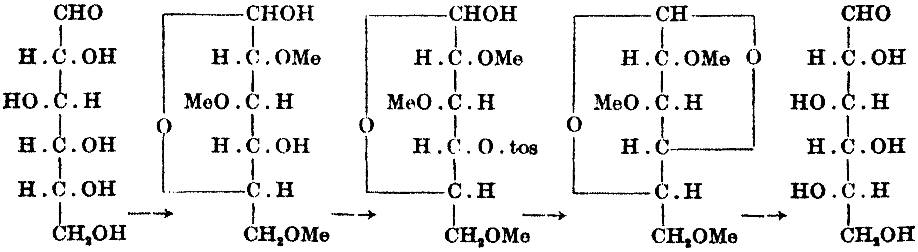


(210)

whilst the ether ring is intact; as soon as hydrolysis takes place glucoseen reverts to *iso*-rhamnose (210).

Space considerations forbid a detailed study of the anhydro- sugars, but the following are important.

(1) *1, 4-Anhydroglucose.*[3]—When D-glucose (211) is converted to its 2, 3, 6-tri-methyl derivative (212), the remaining free hydroxyl group at position '4' can be esterified by the tosyl group [4] (214). The substance so



(211) (212) (213) (214) (215)

obtained is converted by alkali, with elimination of the tosyl group, to the 2, 3, 6-trimethyl-1, 4-anhydro-glucose (214), a substance in which both furanose and pyranose rings are present; demethylation with hydrobromic acid gives L-idose (215).

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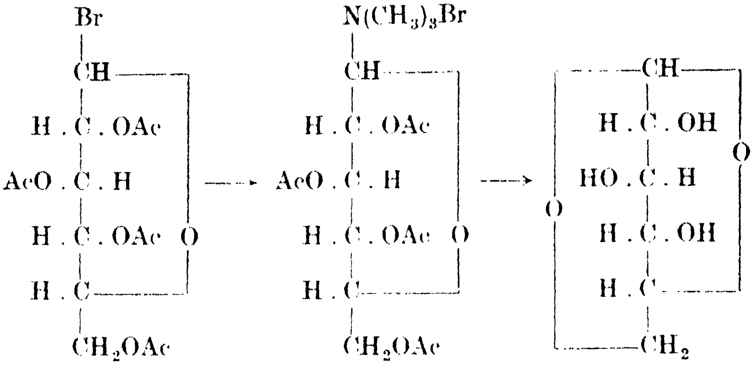
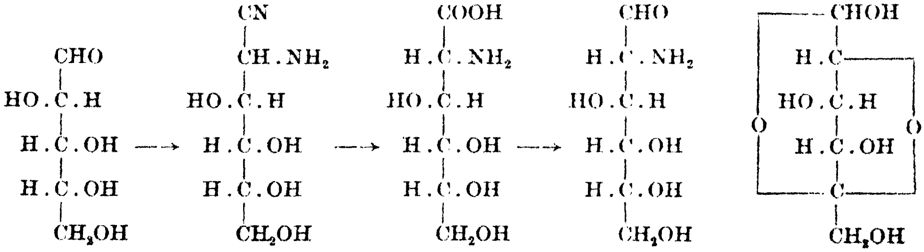
[1] Zerbas, *Ber.*, 1930, **63**, 1689.
[2] Barham and Smits, *Ind. Eng. Chem.*, 1936, **28**, 567.
[3] Hess and Neumann, *Ber.*, 1935, **68**, 1360.
[4] The term 'tosyl' is a convenient abbreviation for '*p*-toluenesulphonyl', ($CH_3 . C_6H_4 . SO_2$—).

(2) *Lævoglucosan, 1, 6-Anhydroglucose.*—First obtained by the distillation of starch *in vacuo*,[1] and also by the following series of reactions from bromo-tetra-acetyl-D-glucose (216) (see also p. 825) which reacts with trimethylamine to give the compound (217); on hydrolysis with alkali, 1, 6-anhydroglucose is formed (218).



(216) (217) (218)

(3) *2, 5- and 3, 6-Anhydroglucose.*—These can be obtained through the medium of the corresponding amino-sugars, a small group of sugar derivatives closely related to the mucoproteins and to chitin, the polysaccharide material of molluscs and insects. The majority of amino-sugars of natural occurrence are 2-aminohexoses, and may be obtained synthetically from the pentose which has structural identity (insofar as the three lower asymmetric carbon atoms are concerned) with the hexose in question. Thus, D-arabinose (219) adds hydrogen cyanide which in the presence of ammonia is converted to the aminonitrile (220).



(219) (220) (221) (222) (223)

This nitrile, when hydrolysed to 2-aminogluconic acid (221), may be reduced via the lactone to the amino-aldose (222) which immediately loses ammonia to give 2, 5-anhydroglucose (223). In practice this sequence of reactions is not quite so simple to operate as the series of formulæ (219 to 223) indicates, since during the addition, an epimeric mixture of D- and L-forms is obtained leading to a mixture of 2-amino-D-gluconic acid with the corresponding D-mannonic derivative; the separation of these two epimers at this stage is essential to the success of the subsequent operations. 3, 6-Anhydroglucose may be obtained from 3-amino-glucose in a similar manner.

Among the various classes of substances obtained from aldose sugars, by loss of the elements of water, the glycals are essentially 'reduced' sugars, since during the dehydration they are deprived also of one atom of oxygen. They are formed when the aldose aceto-bromo compound (224) is allowed to react with zinc in acetic acid ; it appears that the elements of hydrogen bromide and acetyl peroxide are lost and a triacetylglycal (225) formed ; the free glycal (226) is formed when the acetyl groups are removed by hydrolysis. It will be noted

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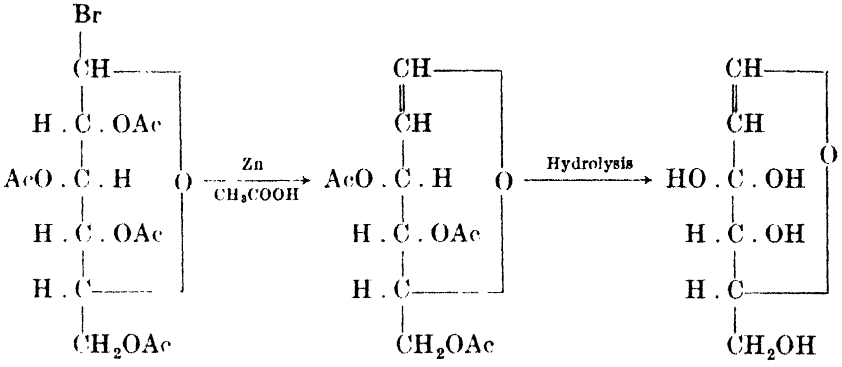
[1] Pictet and Sarasin, *Helv. Chim. Acta*, 1918, 1, 87; 1920, 3, 640.

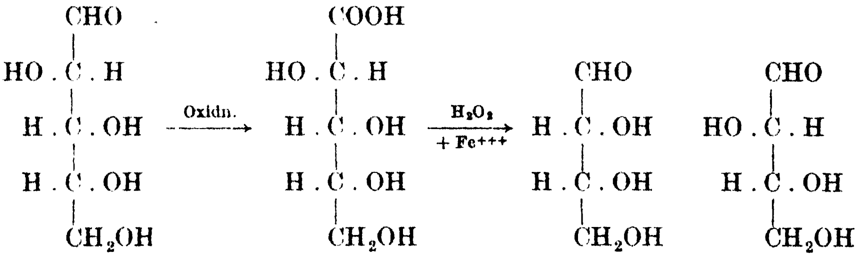


(224) (225) (226)

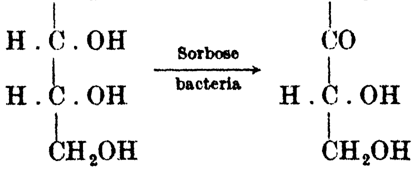
that the essential feature of the glycal is the —CH=CH— structure.[1] Perbenzoic acid oxidation regenerates an aldose from a glycal, by the addition of the elements of hydrogen peroxide ; the aldose formed is not always that from which the glycal was obtained ; the epimer may be formed. Thus, glucal gives mannose, galactal a mixture of talose and galactose in which the former predominates.

SOME INDIVIDUAL SUGARS

The remarks made, so far, in this chapter have related almost entirely to structural problems in simple sugar chemistry, and little has been said concerning the peculiarities of individual sugars. Of the tetroses, two aldotetroses and one ketotetrose are of importance ; D-erythrose (229) is usually made by Ruff's reaction, commencing with D-arabinose (227), which is oxidised to D-arabonic acid (228), the calcium salt of which is converted by hydrogen peroxide and a trace of ferric iron to D-erythrose. D-Threose (229*a*) is obtained by the analogous reactions from D-xylose. D-Erythrulose (231) is obtained by the action of sorbose bacteria on *meso*-erythritol (230).



(227) (228) (229) (229*a*)



(230) (231)

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[1] Bergmann *et al.*, *Ber.*, 1921, **54**, 446 ; 1929, **62**, 2783.

L-*Arabinose* appears to have been obtained first by Biot and Persoz about 1870, by the hydrolysis of gum arabic by dilute sulphuric acid. It caused considerable dissension; Berthelot and Kiliani considered the sugar to be galactose, but Scheibler[1] maintained that it was a new sugar, which he called 'arabinose'. Cherry and plum tree gums, and mesquite gum are richer sources of L-arabinose, and D-arabinose exists as the carbohydrate moiety of barbaloin, and in the urine of morphine addicts. Like all pentose sugars, they give furaldehyde on digestion in hot aqueous/acid solutions (see p. 345). L-Arabinose is strongly dextrorotatory—$[\alpha]_D = +105°$.

D-*Xylose*, often called 'wood-sugar', is available in industrial quantities from the hydrolysis of the lignan of wood and from maize-cobs[2] remaining after the seeds are stripped. This contains a polypentoside, the units of which are D-xylose. The sugar is of interest as the raw material from which Haworth and his co-workers first built up vitamin C (ascorbic acid). Industrially, L-sorbose is used for this synthesis, but a cheaper supply of *d*-xylose might make the original method an economic one. D-Xylose is one of the few pentose sugars with a strong sweet taste; it crystallises in needles, m. 154°.

D-*Ribose*, which forms large prisms, m. 95°, is an almost constant constituent of nucleic acids, and occurs as the carbohydrate portion of the glycoside, crotonoside, which may be extracted from croton-beans. It is an important raw material for the manufacture of riboflavin (see Chap. XII), for which purpose it is prepared from yeast nuclein.

L-*Rhamnose*.—This sugar was originally called 'isodulcite', and was first isolated by Hlasiwetz and Pfaundler from quercitrin.[3] Since then it has been obtained from a very large range of glycosides, including those from lichens (including *Roc. tinctoria*), cardiac glycosides (ouabain, strophanthin, hesperidin, haringin and solanin). L-Rhamnose crystallises easily, and forms a monohydrate, m. 93°; the anhydrous sugar has m.p. 124°. In aqueous solution L-rhamnose is dextrorotatory; in ethanol, lævorotatory, and thus constitutes an additional example of the advantages attending the system of classifying sugars as D- or L- according to the configuration of the lowest asymmetric carbon atom, rather than on optical activity in solution.

L-*Fucose* (L-galactomethylose), is of interest as being the unit of the seaweed and gum tragacanth methylpentosans, and is obtained from them by acid hydrolysis.

D-*Glucose*.—Many early investigators noticed the crystalline sugar-like substance visible in dried raisins, in honey and in the dried unfermented must of grapes. The association of grapes and raisins with this sugar led to its name 'grape-sugar', by which name it was called for many years; Proust in 1802 showed that grape-sugar and the crystalline portion of honey contained the same material. Dumas suggested that, as the sugar was so widely distributed and its incidence was not confined to the grape, it should be called 'glucose'. Berthelot having called the lævorotatory analogue or 'fruit-sugar' 'lævulose'. Kekulé introduced the term 'dextrose' for grape-sugar. The term 'dextrose' is often met with, but a strict adherence to 'D-glucose' is the least confusing terminology.

Apart from its occurrence in plant tissues, glucose is a small but important constituent of animal fluids, being present in the blood, and in abnormal conditions, in the urine. Failure of that portion of the pancreas, known as the islets of Langherans, to secrete insulin leads, in an imperfectly understood manner, to failure to metabolise glucose—which accumulates in the blood, and after a time penetrates the renal membranes and passes into the urine which, in bad cases, may contain 10–12 per cent. of the sugar.

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[1] Scheibler, *Ber.*, 1873, **6**, 614.

[2] Monroe, *J.A.C.S.*, 1919, **41**, 1002.

[3] Hlasiwetz and Pfaundler, *Ann.* 1863, **127**, 362.

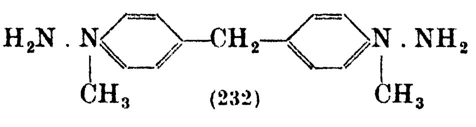
The glucose of commerce is mainly obtained from maize or potato starch. This material when heated under pressure with water containing 1 per cent. of sulphuric acid is largely converted into glucose ; the reaction is never complete under normal conditions, some dextrins (*q.v.*) being formed which retard and, in some cases, entirely prevent crystallisation of the glucose. If the dilute liquid from the hydrolysis be clarified by bone-char and concentrated *in vacuo* a clear, water-white material is obtained, of extremely high viscosity, known as 'confectioner's' or 'w/w' (water-white) glucose ; further removal of water leads to a thick liquid which on cooling increases its viscosity until it appears as a pseudo-solid or 'glass' ; readers will realise the identity of this material with the 'Glacier' type of sweets.

The crystallisation of D-glucose is difficult on a large scale, especially when retarded by the presence of dextrins ; as it normally crystallises, with one molecule of crystal water, the magma of crystals and mother-liquor are almost impossible to separate. On the other hand, if a concentrated solution of D-glucose is seeded at 35–40° with anhydrous glucose crystals a magma is obtained from which the crystals can readily be obtained by use of the centrifuge. They yield a dry granular glucose the crystals of which flow readily, and do not clog together, any slight residual trace of moisture leading to the formation of a small proportion of hydrate.

Ordinary D-glucose is mainly the α-form having an initial $[\alpha]_D = +109{\cdot}6°$ The β-form is best prepared by recrystallising the α- form from boiling pyridine ; its $[\alpha]_D$ is $+20{\cdot}5°$, initially, after standing in solution for a short time both forms show an $[\alpha]_D$ of $+52{\cdot}5°$, this representing the equilibrium position for the change, $\alpha \rightleftharpoons \beta$.

L-Glucose is only known as a synthetic material made by Kiliani's method from L-arabinose. It is unfermented by yeast.

D-*Mannose* is the unit of the high-molecular weight mannans, such as 'seminine', of the ivory nut (*Phytelephas macrocarpa*),[1] from which it may be obtained by prolonged hydrolysis of the finely ground nut ; it is present in yeast and certain types of seaweed. It melts at 132°, and is readily separated from solution through its comparatively insoluble but readily recrystallised phenylhydrazone ; it gives an osazone which, it has already been remarked, is identical with that of D-glucose. D-Mannose reacts with v. Braun's epimer reagent, thus differing from *d*-glucose. The epimer separation of v. Braun is


(232)

based on the fact that *bis*-4, 4′-(α-N-methyl-hydrazino)diphenylmethane (232) will react only with aldoses in which an adjacent pair of the 2, 3 and 4 carbon

+	—	—	+
—	—	+	+
+	+	—	—
+	+	+	+
D-Glucose	D-Mannose	D-Idose	D-Gulose

atoms are of the same sign. Thus, D-glucose does not comply with this requirement ; D-mannose does, and can combine. The reaction is also capable of separating idose and gulose.

D-*Galactose* is one of the few hexose sugars readily available—as it can be obtained with considerable ease from the hydrolysis of lactose. It forms the unit of a group of polymers—the 'galactans', which occur in seeds of many types; it is a frequent partner of other sugars in the simple polysaccharides, and occurs in many conjugated proteins.

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[1] Horton, *J. Ind. Eng. Chem.*, 1921, **13**, 1040.

The remaining aldose sugars are mainly of academic interest, and need not be further described; their structures are given in an earlier portion of this chapter.

The Oligosaccharides

The term 'oligosaccharide' was coined by Freudenberg to distinguish those simple polysaccharides such as the di-, tri- and tetrasaccharides from the starches, celluloses and related compounds. The main oligosaccharides are listed in Table VI.

It will be observed from Table VI that at least seven di-saccharides (framed in the table) are simple compounds of two molecules of D-glucose; since they are isomeric, the differences between them must lie in the position of the bond connecting the glucose molecules. The methods by which the position of these bonds is demonstrated, are mainly concerned with methylation and subsequent hydrolysis of the methylated sugars so obtained.

Maltose.—In 1811 Kirchoff first obtained maltose by cautious acid hydrolysis of starch; and he also made the observation [1] that the conversion of starch to maltose could be effected more readily by malted grain. Saussure [2] made further investigations on maltose in 1819, but it remained for Dubrunfaut [3] to recognise it as a distinct sugar, different from grape-sugar, having a lower solubility in alcohol, and a higher optical rotatory power.

Recognition of the fact that maltose was composed of two glucose molecules joined through the loss of the elements of a molecule of water, was due to Meissl.[4] The position of the link between the two moieties remained unsolved, until the investigations of Haworth and his co-workers during the third decade of this century. In 1919 [5] it was found that the molecule of maltose could take up eight methyl groups; the substance so obtained is termed 'methyl-heptamethylmaltoside' (not 'octamethyl-maltose'), since one methyl group differs from the others in lability, and is clearly analogous to the methyl group of α- or β-methylglucoside. Since only one such group is found it is deduced that one glucose residue is joined to the other through the '1' carbon atom. On hydrolysing methylheptamethylmaltose, two crystalline methylated sugars can be obtained—2, 3, 4, 6-tetramethylglucose and 2, 3, 6-trimethylglucose (234 and 235). Assuming, for a moment, that we are justified in using the pyranose formula for D-glucose, it is clear that since 2, 3, 4, 6-tetramethylglucose has only one free hydroxyl group, attachment must have taken place through the carbon atom '1' (marked * in 234); in 2, 3, 6-trimethylglucose there are two free hydroxyl groups; one, on the '1' carbon atom must remain for the labile eighth methyl group, hence the other '4' carbon must be the point of attachment. The structure of methyl-heptamethylmaltoside will be shown by (236), the methyl group marked (*) being the labile glycoside group. Maltose will, therefore, have the structure (237) of a 4-D-glucopyranosyl-α-D-glucopyranoside. The assumption has, of course, been made that both rings are pyranose in structure; this appears inevitable in respect of that half of the molecule from which the tetramethylglucose is ultimately obtained, but an ambiguity arises in the moiety giving 2, 3, 6-trimethylglucose; if the ring structure of this half had

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[1] Kirchoff, *C.R.*, 1813, **14**, 389.

[2] Saussure, *Ann. Chim. Phys.*, 1819, **11**, 379.

[3] Dubrunfaut, *ibid.*, 1847 [3], **21**, 178.

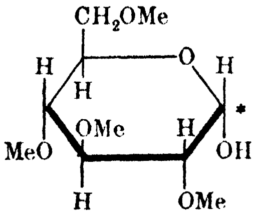
[4] Meissl, *J. Pr. Chem.*, 1882 [2], **25**, 123.

[5] Haworth and Leitch, *J.C.S.*, 1919, **115**, 809.

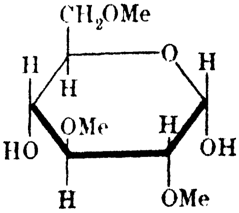
TABLE VI

Name	Redn. of Fehling's soln.	No. of mono-saccharide units	Monosaccharide units	M.P.	[α]$_D$	Source
Vicianose		2	D-glucose + L-arabinose			Vetches
Primeverose		2	D-glucose + D-xylose			Primrose and tree-bark
Rutinose		2	D-glucose + L-rhamnose			
Sucrose		2	D-glucose + D-fructose	160°	+ 66·5°	Sugar beet, sugar cane
Turanose		2	D-glucose + D-fructose	157°	+ 75·6°	Melezitose
Trehalose **Isotrehalose** **Neotrehalose**		2	D-glucose + D-glucose		+ 197°	Trehalamanna Reserve carbohydrate of fungi *B. Lepra*
Maltose	+	2	D-glucose + D-glucose		+ 137°	Malt ; synthesis from glucose
Revertose		2	D-glucose + D-glucose			
Cellobiose	+	2	D-glucose + D-glucose		+ 34·6°	Cellulose
Gentiobiose		2	D-glucose + D-glucose	190°	+ 9·8°	Gentianose
Lactose	+	2	D-glucose + D-galactose		+ 55·3°	Milk
Melibiose	+	2	D-glucose + D-galactose		+ 143°	Melitriose
Raffinose	—	3	D-glucose + D-galactose + D-fructose		+ 104°	Beet molasses Cottonseed meal Eucalypt. manna
Gentianose	—	3	2[D-glucose] + D-fructose			
Melezitose	—	3	2[D-glucose] + D-fructose			
Mannotriose	+	3	D-glucose + 2[D-galactose]			
Stachyose	—	4	D-glucose + 2[D-galactose] + D-fructose		+ 149°	

been furanose in character, and attachment to the other half through the ' 5 ' carbon atom, the same trimethylglucose would have been obtained by the steps previously outlined. This ambiguity was removed by the work of



(234)



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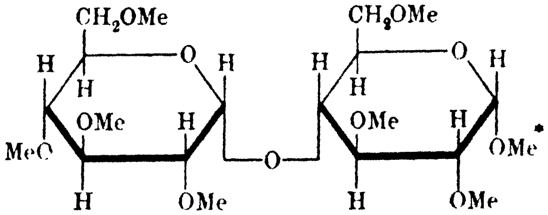

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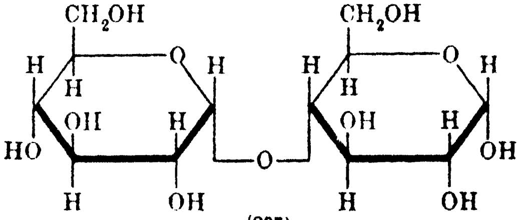

(237)

Haworth and Peat,[1] who oxidised maltose to maltobionic acid (238), which on methylation gives a methyloctamethylmaltobionate (239), and this on hydrolysis gives methanol, 2, 3, 4, 6-tetramethyl-glucose (240) and 2, 3, 5, 6-tetramethyl-gluconic acid (241), thus clinching the point of linkage of the second half, through the ' 4 ' carbon atom.

Gentiobiose.—This sugar, which is also derived from two glucose molecules, has been shown to be the disaccharide of amygdalin, the glycoside of bitter almonds. This was first indicated by Hudson [2] and later synthesis [3] showed amygdalin to be L-mandelonitrile-β-gentiobioside. Bergmann and Freudenberg [4] obtained a gentiobiose octa-acetate from amygdalin, thus confirming the previous evidence.

Gentiobiose is also obtained from the tri-saccharide gentianose, isolated some sixty years ago from *Gentiana lutea* roots. The structure of gentianose is not elucidated with certainty, but on hydrolysis with enzymes, or by very dilute acids, it yields the disaccharide gentiobiose and a molecule of D-fructose. Gentiobiose, on further splitting by emulsin, gave two molecules of D-glucose ; that this reaction is reversible, and may be used for the synthesis of gentiobiose from D-glucose was an important contribution to biochemistry made by Bourquelot in 1913.[1]

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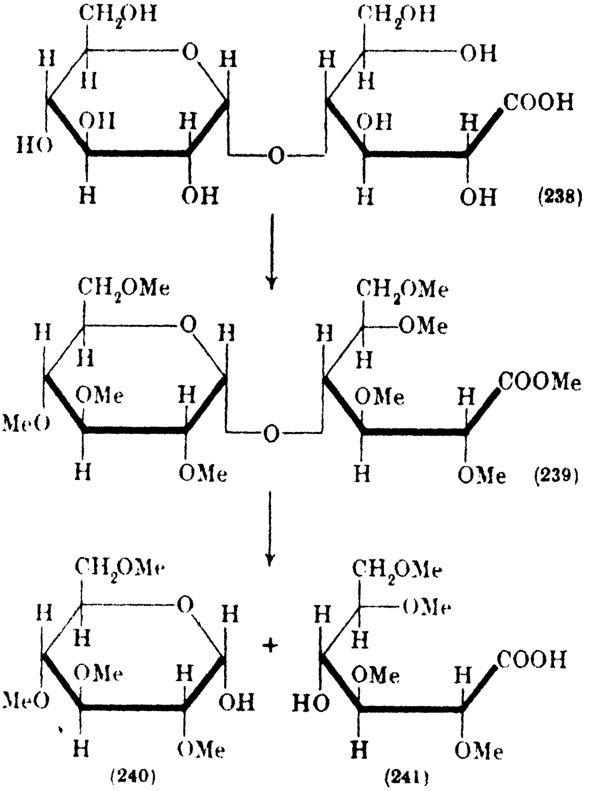
[1] Haworth and Peat, *J.C.S.*, 1926, 3094.
[2] Hudson, *J.A.C.S.*, 1924, **46**, 483.
[3] Campbell and Haworth, *J.C.S.*, 1924, **125**, 1337.
[4] Bergmann and Freudenberg, *Ber.*, 1929, **62**, 2783.

When D-glucose is re-synthesised to a disaccharide by maltase, a new sugar, 'revertose', is formed, the structure of which is not yet fully established.



Haworth's classical method of structure determination gave, with gentiobiose[2] a methylheptamethylgentiobioside (242), a substance which gave on hydrolysis:

i. Methanol, indicating a free '1' hydroxyl in the original sugar.
ii. 2, 3, 4, 6-Tetramethylglucose (243), indicating a normal pyranose glucose moiety in gentiobiose, linked through the '1' carbon.
iii. 2, 3, 4-Trimethylglucose (244), indicating a second glucose moiety which must be linked through the '6' carbon if the normal pyranose ring is present.

This gives (245) as a working hypothesis for the structure of gentiobiose, although it implies the existence of a 1, 5- and not a 1, 6-ring in the second moiety; the semi-systematic name of gentiobiose on this hypothesis would be 6-D-glucopyranosyl-β-D-glucopyranoside. The structure has been confirmed by the work of Helferich, who has summarised his work in a general review.[3] Briefly, he was able to obtain an acetylated glucose in which the '6'- position alone was free (246); this reacted with acetobromoglucose (247) to give gentiobiose octa-acetate (248), thus clearing up any ambiguity concerning the '6' link. The 1, 2, 3, 4-tetra-acetylglucose was obtained by taking advantage of the tendency which tritylchloride * shows for reacting with primary alcohol groups, enabling a 6-monotritylglucose to be obtained (249) ; this was acetylated (250) and the trityl group removed, by taking advantage of the fact that dilute hydrobromic acid will hydrolyse the trityl group without affecting the acetyl groups.

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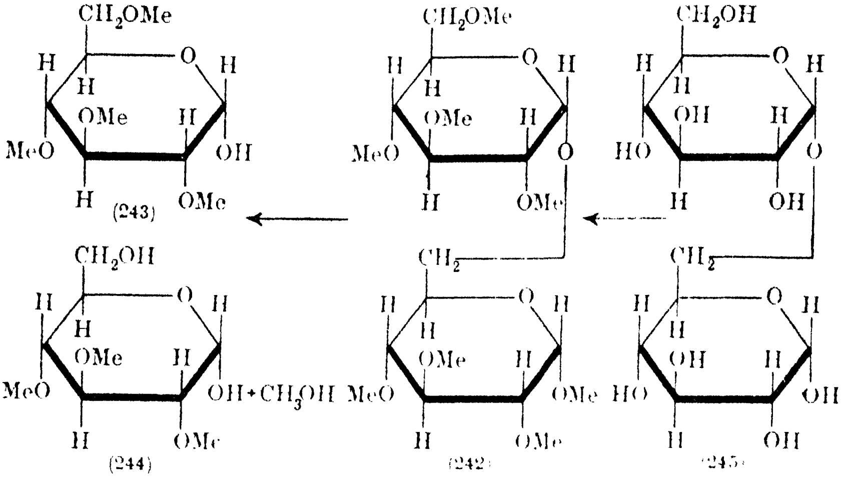
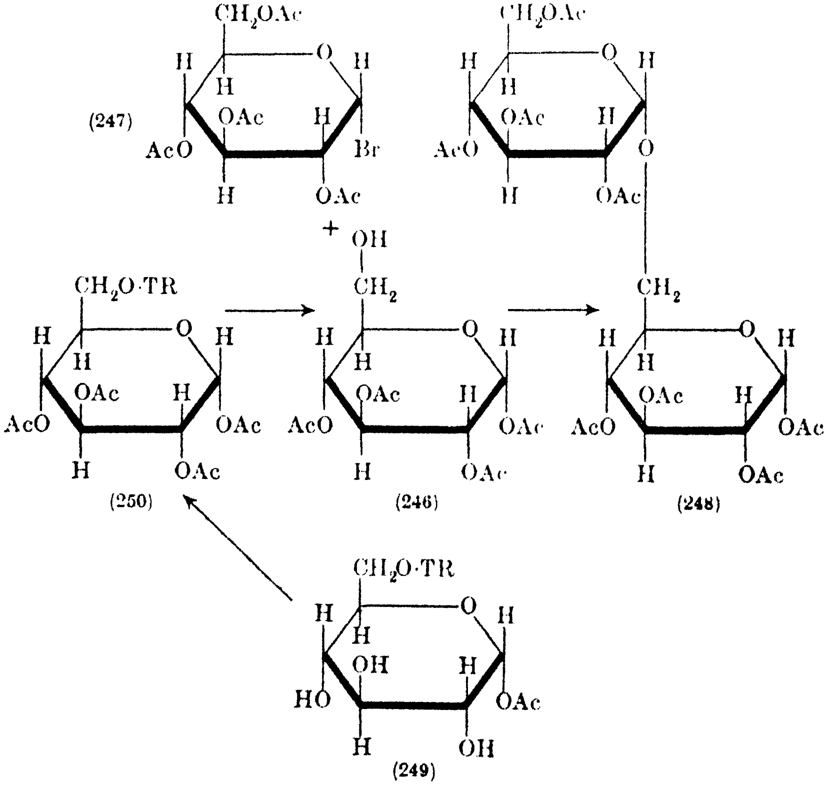
[1] Bourquelot, Hérissey and Coire, *C.R.*, 1913, **157**, 732.
[2] Haworth and Wylam, *J.C.S.*, 1923, **123**, 3120.
[3] *Z. Angew. Chem.* 1928, **41**, 871.





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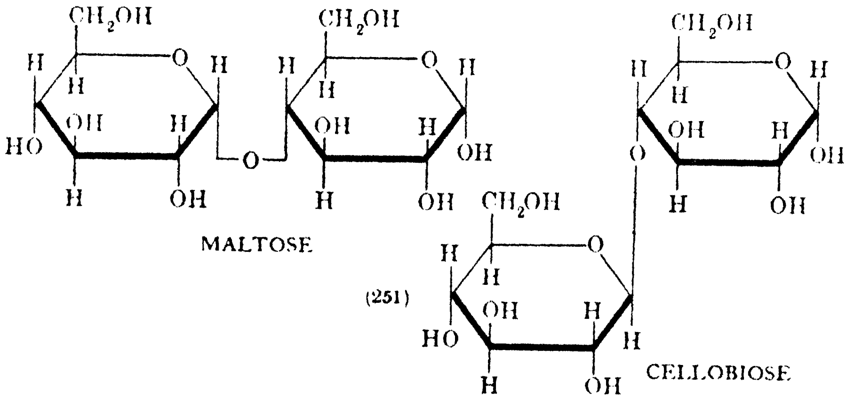
* ' Trityl chloride —an abbreviated form of ' triphenylmethylchloride ', Ph_3C . Cl.

Cellobiose.—Sixty-nine years ago Franchimont,[1] in experimenting on the formation of acetyl-cellulose, discovered that a crystalline body of comparatively low molecular size could be obtained by the persistent action of acetic anhydride and sulphuric acid on cellulose. This crystalline substance was proved, much later, to be cellobiose octa-acetate from which Skraup[2] and his co-workers isolated the sugar cellobiose itself.

The crystalline sugar has properties similar to those of most disaccharides; when subjected to the process of methylation and hydrolysis[3] it yields exactly the same 2, 3, 4, 6-tetramethylglucose and 2, 3, 6-trimethylglucose, as does maltose; and when oxidised the octamethylcellobionate behaves, on hydrolysis, in an exactly analogous way to that of octamethylmaltobionate, giving 2, 3, 4, 6-tetramethylglucose and 2, 3, 5, 6-tetramethylgluconic acid. Thus, we have two sugars, maltose and cellobiose, giving the same methylation and hydrolytic products; this means that maltose and cellobiose are formed from identical D-glucopyranose units joined through the same carbon atoms; their only point of structural difference must reside in the stereochemical relation of the linkage—they are α- and β- glycosides. The assignment of α- and β- structures to maltose and cellobiose respectively is made on the basis of Fischer's observations on the specificity of enzyme action, α-glycosides exclusively being hydrolysed by maltase and β-glycosides by emulsin. Since maltose and cellobiose are hydrolysed by maltase and emulsin respectively, it follows that their structures must have the configurations conventionally indicated in (251). Cellobiose has been synthesised.[4]



(251)

The Trehalose Group.—The three sugars of this group are built up by fungi, mainly as reserve food; although known for over a century, trehalose itself has attracted little attention. Trehalose was first isolated in 1833 by Wiggers from ergot of rye (*Claviceps purpurea*); the name 'trehalose' is derived from 'trehala manna'; certain insects (*Lavinus nidificans*) feed on a species of *Echinops* indigenous to Syria and regurgitate the partly digested food as a nest-building material; it is, in effect, crude trehalose,[5] and is an article of commerce in the East as 'trehala manna' or 'nest-sugar'. Simple extraction with hot alcohol and recrystallisation yields large rhombic crystals of trehalose, which hold two molecules of water of crystallisation. It has a sweet taste, but no reducing function and has no free, active glycosidal function. Its two glucose fragments must, therefore, be joined through the '1' carbon atoms.

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[1] Franchimont, *Ber.*, 1879, **12**, 1941.

[2] Skraup and König, *ibid.*, 1901, **34**, 1115.

[3] Haworth *et al.*, *J.C.S.*, 1921, **119**, 193; 1927, 2809.

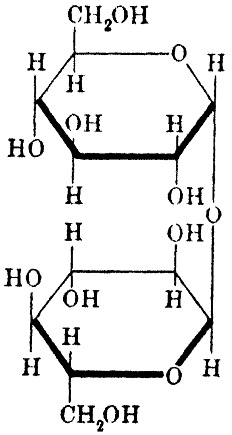
[4] Ionescu and Kizyk, *Bul. Soc. chim. România*, 1935, **17**, 283.

[5] Freudenberg and Nagai, *Ber.*, 1933, **66B**, 27.

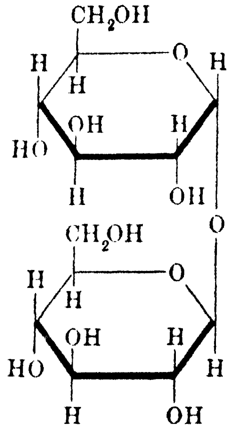
iso-Trehalose is formed when phosphorus pentoxide acts upon a chloroform solution of 2, 3, 4, 6-tetra-acetyl-*d*-glucose,[1] and the resultant octamethyl-*iso*-trehalose is demethylated; it is chemically very similar to trehalose, but is lævorotatory.

neo-Trehalose is obtained when the dehydration of the tetramethylglucose referred to above is carried out with zinc chloride at 140°, when octamethyl-*neo*-trehalose is obtained.[2]

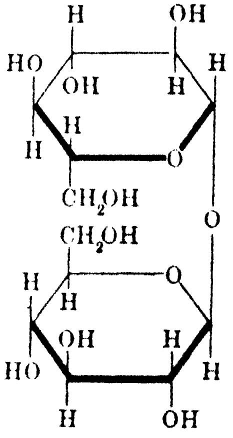
All three trehaloses are non-reducing, and have no free glycosidal function. They represent, therefore, the αα-, αβ- and ββ- forms of 1-D-glucopyranosyl-D-glucopyranoside, conventional representations of which are given in (252 to 254). All forms give an octamethyl trehalose which, on hydrolysis, is converted into two molecules of 2, 3, 4, 6-tetramethylglucose. The assignment of these three structures to the three trehaloses rests to a large extent on the application of Hudson's calculations concerning rotatory power[3] (see also Vol. III, Chap. IV) from which the conclusion is drawn that ordinary trehalose is the αα- form, *iso*-trehalose the ββ- form and *neo*-trehalose the αβ- form.



αα (252)



αβ (253)



ββ (254)

It will have been observed that the structural hypotheses set out in previous pages, concerning the structure of the disaccharides, all depend on the ability of the investigators to recognise the various methylated hexoses. The establishment of the structure of 2, 3, 4, 6-tetramethylglucose has already been discussed (p. 787); the structure of some of the remaining methyl-hexoses must now be discussed.

2, 3, 6-Trimethylglucose.—This substance (255) is obtained during the hydrolysis of methylated disaccharides and also from the hydrolysis of methylcellulose. The fact that it gives 2, 3, 4, 6-tetramethylglucose on further methylation (256)[4] confirms the presence of the pyranose ring; the fact that this trimethylglucose gives no osazone indicates that one methyl group is attached at the '2' position; on oxidation, a dimethylsaccharic acid (257) is obtained[5] which indicates that one of the methyl groups is attached to the '6'-position. The evidence on which the third methyl group is assigned to the '3'-position, involves a consideration of the behaviour of the acid obtained by carrying out Kiliani's reaction on the trimethyl-glucose (255). When this acid (258) forms a lactone ring, demethylation takes place, and since it is highly probable that the lactone ring is pyranose (259) it follows that the '3' carbon of the original trimethylglucose must have

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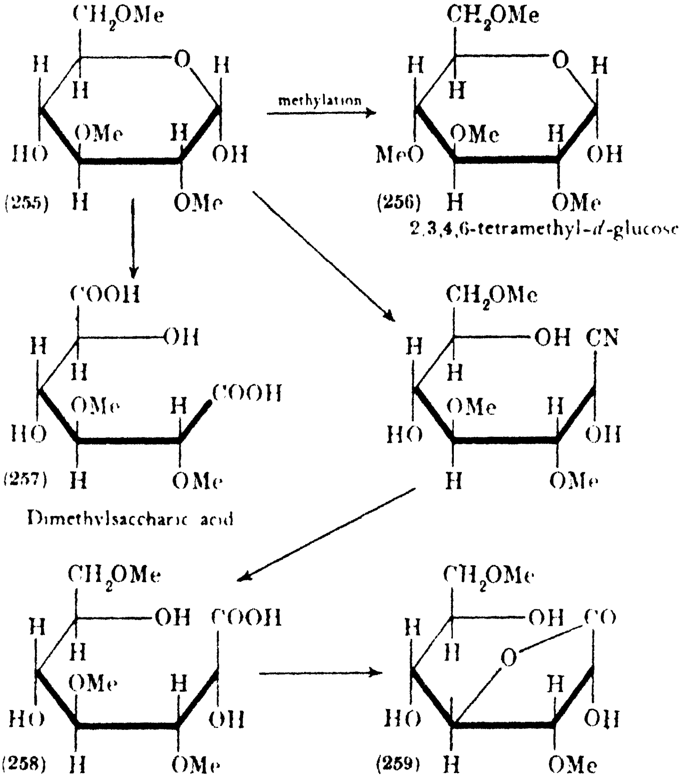
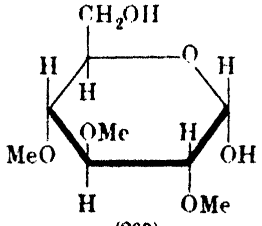
[1] Fischer and Delbrück, *Ber.*, 1909, **42**, 2776.
[2] Schlubach and Maurer, *ibid.*, 1925, **58** [B], 1178.
[3] Hudson, *J.A.C.S.*, 1916, **38**, 1571.
[4] Haworth and Hirst, *J.C.S.*, 1921, **119**, 193.
[5] Irvine and Hirst, *ibid.*, 1922, **121**, 1213.

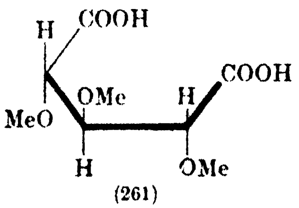


carried a methoxy group. Other confirmatory evidence on this point was obtained by Haworth and Leitch[1] from consideration of the degradation of lactose.

2, 3, 4-Trimethyl-d-glucose.—The fact that this trimethylglucose gives 2, 3, 4, 6-tetramethyl-D-glucose on methylation, and *i*-xylotrimethoxyglutaric



(260)



(261)

acid derivatives (261) on oxidation[2] indicates that it must have the 2, 3, 4-trimethyl structure (260).

*2, 3, 4, 6-Tetramethyl-*D*-galactose*.—This sugar is usually isolated and purified through its easily crystalline anilide. Inasmuch as it has the normal glycosidal function and four methyl groups the only point of doubt is as to the pyranose nature of the ring; this was confirmed by Howarth *et al*, who converted it to the crystalline methylamide of L-arabotrimethoxyglutaric acid (263), thus showing that the ring must be pyranose (262).

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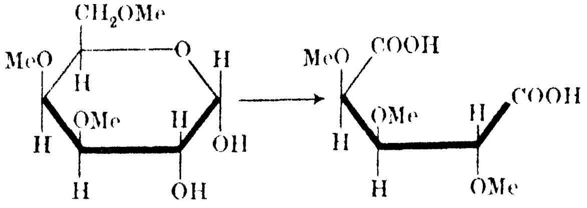
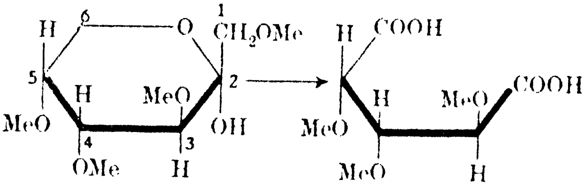
[1] Haworth and Leitch, *J.C.S.*, 1918, 113, 197.

[2] Charlton, Haworth and Herbert, *ibid.*, 1931, 2885.



(262) (263)

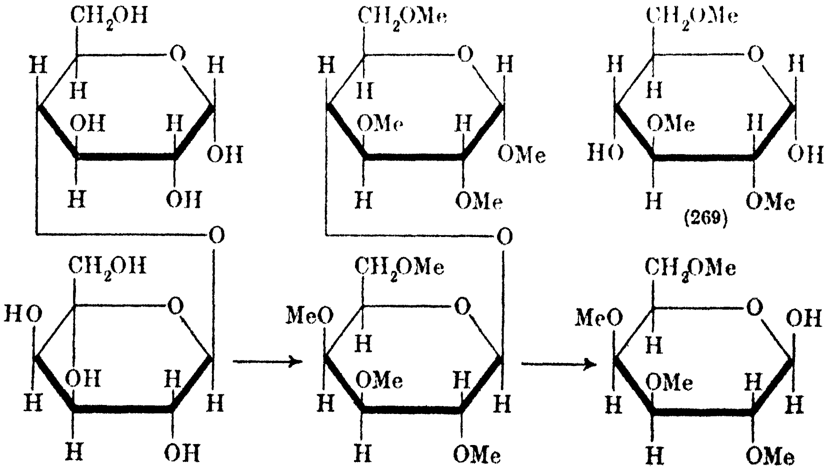
Tetramethyl-D-fructopyranose.—This sugar is particularly important in connexion with the structure of normal D-fructose. When tetramethylfructose is oxidised it is possible to isolate the methyl amide of D-arabotrimethoxyglutaric acid (264); since the structure of D-fructose is known and contains the same



(264) (265)

— + + configuration on the 3, 4 and 5 carbon atoms, it follows that the ring must be between carbons '2' and '6'. Hence the substance is 1, 3, 4, 5-tetramethyl-δ-gluco-pyranose. This is in contrast to the tetramethylfructofuranose from methylated sucrose.

The Structure of Lactose.—There are several sugars present in milk [1] of which lactose (266) represents over 90 per cent. It reduces Fehling's solution and yields one molecule each of D-glucose and D-galactose on hydrolysis. The method



(266) (267) (268)

of Haworth [2] was applied with conspicuous success to the study of the structure of lactose. On methylation lactose gives a methylheptamethyllactoside (267) which on hydrolysis yields 2, 3, 4, 6-tetramethylgalactose (268) and 2, 3, 6-trimethyl-glucose (269).

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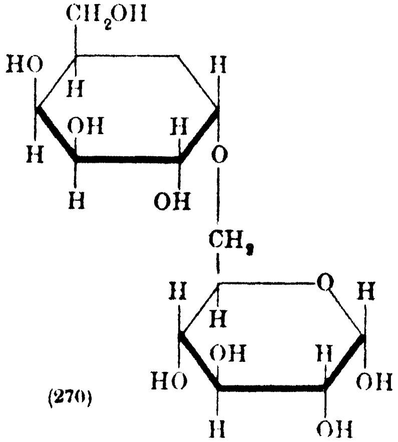
[1] Polonovski and Lespagnol, *C.R. soc. biol.*, 1930, **104**, 553.

[2] Haworth and Long, *J.C.S.*, 1918, **113**, 188.

This leaves the position of the connecting link ambiguous; oxidation of lactose to lactobionic acid and methylation, followed by hydrolysis gives the same tetramethylgalactose, together with the lactone of 2, 3, 5, 6-tetramethylgluconic acid, thus confirming the presence of a pyranose ring and the linkage of the two hexose moieties through the '4' carbon of glucose.

Melibiose has been shown by methods entirely analogous to those already discussed above, to be 6-α-galactosido-α-glucopyranose (270). It is rarely met with, being a breakdown product of raffinose, a trisaccharide.



(270)

Sucrose.—Reference has been made, in the introduction to this chapter, to the antiquity of the use of sucrose. It is present in a wide range of plants in addition to the sugar-cane and sugar-beet and is widely distributed in seeds; it is present in certain kinds of honey—and the honey receptacles of the *Rhododendron ponticum* are often filled with crystalline sucrose. The manufacture of sugar has become a considerable industry, and its utilisation constitutes an extensive technology.

The structure of sucrose proved more difficult to elucidate than those of the purely aldose sugars, partly because of the initial lack of knowledge concerning the methyl fructoses. When sucrose is methylated by the procedure of Haworth, it yields a heptamethylsucrose, and only with difficulty is the eighth methyl group introduced, giving an octamethyl-sucrose, in which no glycosidic methyl group is apparent; this fact taken together with the non-reducing nature of sucrose, proves that the points of attachment of the glucose and fructose moieties are the '1' and '2' carbon atoms respectively. When the octamethylsucrose is hydrolysed 2, 3, 4, 6-tetramethylglucose is formed (273), together with a tetramethylfructose (274) which differs markedly from the 1, 3, 4, 5-tetramethylfructose (p. 820) encountered in determining the ring structure of fructose itself. It follows, therefore, that the ring present in the fructose moiety of sucrose is different from the pyranose (2, 6) ring of free fructose. The identification of the ring as a furanose structure depends[1] on oxidation of the new tetramethylfructose. Oxidation with dilute nitric acid led to a carboxylic acid (275) indicating (since one methyl group is lost in the process) a terminal '1' methyl group. Oxidation of this acid with barium permanganate and dilute sulphuric acid gave the crystalline and already known trimethyl-D-arabino-γ-lactone (276), and this in turn could be oxidised to the *lævo*-rotatory dimethoxysuccinic acid (277), thus confirming the furanose structure of sucrose (271) and its octamethyl derivative (272). A sugar closely related to sucrose is *turanose* which like sucrose is hydrolysed to an equimolecular mixture of D-glucose and D-fructose. Unlike sucrose, however, it reduces Fehling's solution and has one glycosidic function free. It appears that the ring structure of the fructose moiety has not been finally determined but it is probable that turanose is the 6-glucopyranosyl-γ-fructose (278).

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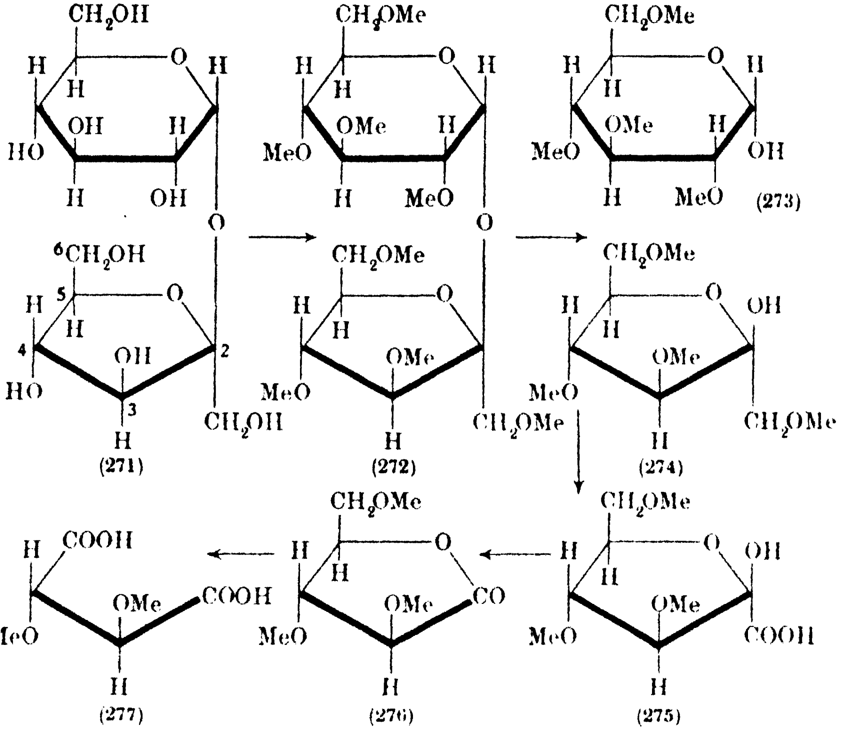
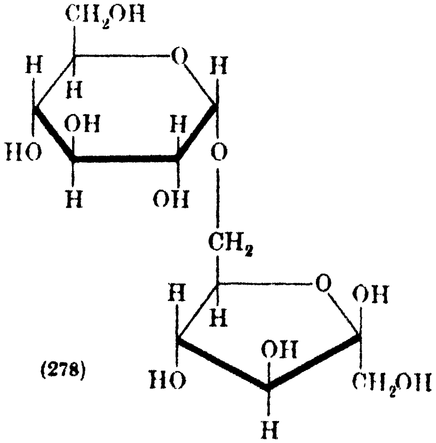
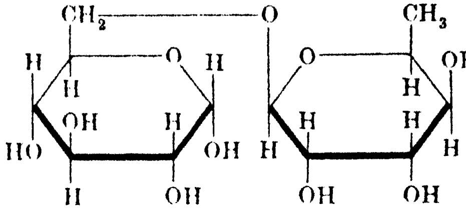
[1] Avery, Haworth and Hirst, *J.C.S.*, 1927, 2308.




(278)

There is also a small group of disaccharides, the structure of which unites a molecule of D-glucose with a pentose unit; thus rutinose is obtained from rutin, one of the glycosides of quercetin. Methylation studies show it to be L-rhamnosido-6-D-glucose, probably (279). In addition, primeverose was shown by

Helferich and Rauch[1] to have the structure of 6-xylosidoglucose (280); vicianose is a similar combination of D-glucose and L-arabinose.



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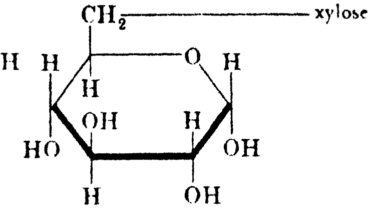
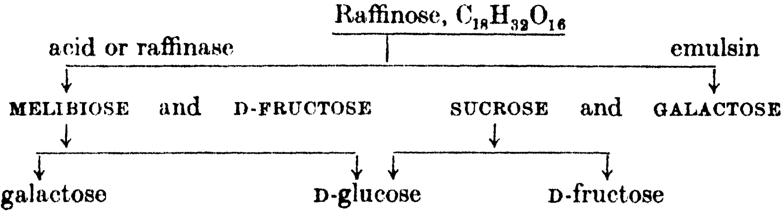
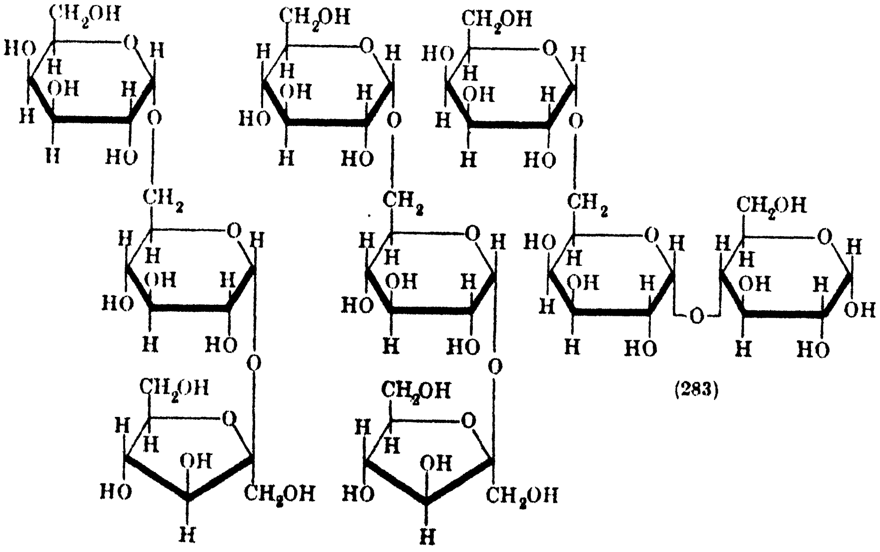


(280)

TRI- AND TETRASACCHARIDES

Raffinose, or melitriose, was discovered in molasses, and is especially plentiful in those from beet; it also occurs in cottonseed meal, from which one twelfth of its weight can be recovered as pure raffinose. Although crystalline, raffinose is tasteless. The breakdown of raffinose by enzymes, as shown below, indicates that the three units, D-glucose, D-fructose and D-galactose are united as in sucrose and melibiose. The fact that there is no reducing power or free glycosidic function in raffinose indicates that the three hexose moieties are all bound through the glycosidic carbon atoms, '1' in the case of D-glucose and D-galactose,





(281) (282) (283)

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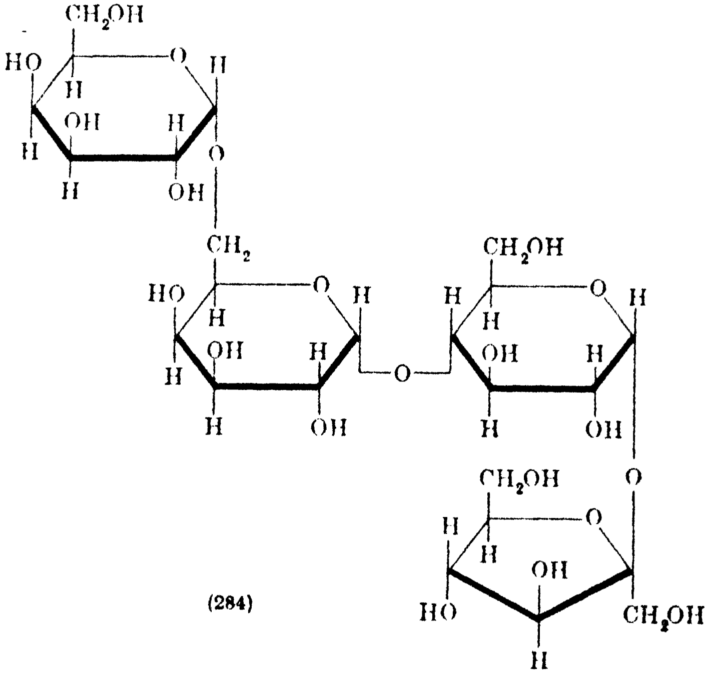
[1] Helferich and Rauch, *Ann.*, 1927, 455, 168.

and '2' in the case of D-fructose. Haworth *et al*,[1] completed the investigation of the structure of raffinose by converting it to undecamethyl-raffinose, which broke down on hydrolysis to 2, 3, 4, 6-tetramethylgalactopyranose, 1, 3, 4, 6-tetramethylfructofuranose and 2, 3, 4-trimethylglucopyranose. These facts, taken together with the known structure of sucrose and meliobiose, are a clear indication of the structure (281) for raffinose, glucose constituting the inner moiety.

Gentianose, which gives rise to gentiobiose and D-fructose, is also without an active glycosidic function, and is probably a L-fructosido-6-glucosidoglucose (282). Melezitose is a trisaccharide from larch manna,[2] hydrolysed to D-glucose and turanose; and mannotriose gives two molecules of galactose and one of glucose. It reduces Fehling's solution and gives methylated hydrolytic products which indicate that it has the structure of a 6-galactosido-1-glucosidogalactose (283).

Only one tetrasaccharide of importance has been examined, namely, stachyose, $C_{24}H_{42}O_{21}$, originally isolated from the root of the plant *Stachys tubifera*, and which on cautious hydrolysis yields mannotriose and D-fructose. A study of the fully methylated stachyose by Omiki indicated that its methylated hydrolytic products are consistent with the structure (284) in which the double galactosido-glucoside is coupled with D-fructose. Stachyose has no reducing properties.



(284)

Much has been said in the previous paragraphs about the breakdown products of polysaccharides, but so far little has been said about their synthesis. It is a matter of some difficulty to induce combination between the two hexose moieties of a disaccharide, although the process is readily carried out by enzyme action. Thus, Hérissey[3] has shown that gentiobiose, cellobiose and lactobioses can be obtained by the action of emulsin on concentrated solutions of the appropriate hexose sugars.

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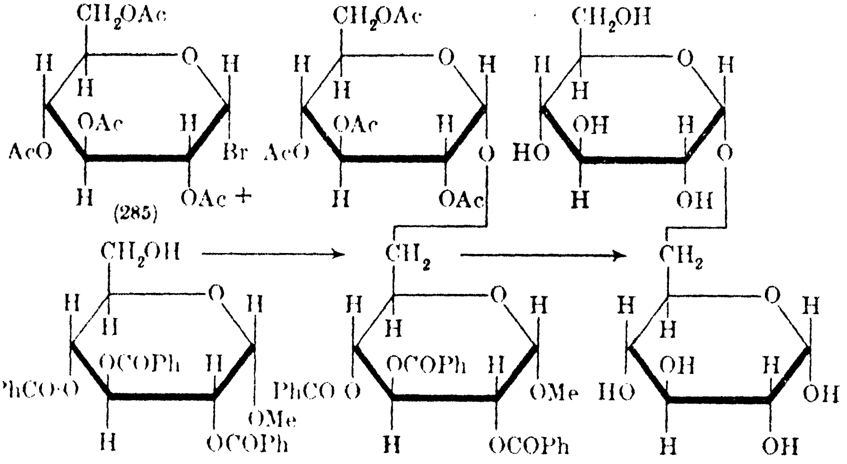
[1] Haworth, Hirst and Ruell, *J.C.S.*, 1923, **123**, 3125.
[2] Bonastre, *J. de Pharm.*, 1833, Tom. II, 19, 443.
[3] Hérissey, 'Les glucosides', *Bull. Soc. Chim.*, 1923 [4], **33**, 349.

Chemical methods of synthesis have been applied to a few disaccharides only, mainly by the route devised by Fischer in which acetobromo-glucose is allowed to react with hexose sugars in faintly alkaline solution. The disadvantage of this procedure lies in the tendency of the acetylbromoglucose to couple with the free glucose molecule at several different points giving a mixture of sugars. Helferich uses, as the second component in this synthesis, a partly benzoylated methylglucoside with only one free hydroxyl group, thus eliminating any ambiguity. Thus, if aceto-bromoglucose (285) and methyl (2, 3, 4-tribenzoyl) glucoside (286) are condensed in alkaline solution, a methylglycoside of tribenzoyltetracetylgentiobiose (287) is obtained from which gentiobiose (288) is obtainable by hydrolysis. Biosyntheses calculated to obtain sucrose have recently proved successful; Doudoroff, Barker and Hassid, of the University of California, having obtained sucrose, identical with the natural material, by the action of an enzyme from *Pseudomonas saccharophila* on a mixture of fructose and glucose phosphate.



(285) (286) (287) (288)

The High Molecular Polyoses

The field of amorphous polyoses of high molecular weight is best divided into the following sections :—

(1) The starches.
(2) The hemicelluloses.
(3) Cellulose.
(4) Lignin.
(5) Pectins, plant-gums and mucilages.
(6) Animal carbohydrates, including chitin, bacterial carbohydrates, glycogen, galactogen.

The Starches

Starch has been known as a valuable material of industry for a long time, the Greeks called it ʻ αμυλον ʼ from which we derive the name " amylose " given to certain portions of the starch grain. (The Greek word means literally ʻ without millstone ʼ, and is a reference to the fact that this fine flour-like material could be obtained without recourse to grinding.) Starch is widely distributed through the vegetable and animal kingdom, where it forms a reserve of carbohydrate material. The deposition of starch granules in vegetable tissue is closely associated with the function of chlorophyll, and in cryptogams which do not contain chlorophyll, starch is not present in any considerable amount.

The main type of starch met with is that occurring in vegetable matter and giving glucose on hydrolysis; this is the material commonly referred to as 'starch'; inulin is a starch which is also fairly widely distributed in vegetation, and which gives D-fructose on hydrolysis; a different starch of the D-fructose group is phlein in which the D-fructose units are differently linked. A mannose polymer, mannan, is found in the tubers of *Eonophallus Konjaku*. Among the animal starches, glycogen is the most important, although snails are able to build up reserve carbohydrate into a galactose-starch, known as 'galactogen'. The main features of the common starches are shown in Table VII.

TABLE VII

Name	Source	Sugar units	Properties
Amylose	General in plants	D-glucose	Blue starch reaction
Amylopectin	General in plants	D-glucose	Red-violet starch reaction (may contain some phosphate ester)
Inulin	Dahlia tubers; *Compositae* generally	D-fructose	$[\alpha]_D^{20}$ — 40°. Non-reducing
Phlein	Tubers of *Phleum pratense* grass	D-fructose	
Asparagosin Sinistrin Graminin	Asparagus	D-fructose	Branched-chain starches similar to inulin
Lævan Roain Recalin	Yucca Jerusalem antichoke	D-fructose	Non-arborescent starches similar to phlein
Mannan	Japanese konjak-flour	D-mannose and D-glucose	$[\alpha]_D^{20} = +42{\cdot}8°$
Glycogen	Animal tissues	D-glucose	$[\alpha]_D$ *ca.* 197°
Galactogen	Snails (*Helix pomatia*)	D-galactose	$[\alpha]_D^{20} = -20°$

Starch grains are not homogeneous; they consist of a central nucleus surrounded by concentric layers which are quite easily visible in starch which has been heated; Meyer[1] suggested that the differences in density and optical properties between the portions of the starch granule are due to the day and night cycle in the plant growth. The size, shape and behaviour of the starch granules under polarised light are valuable aids to identification. The composition of starch grains is, again, heterogeneous; there is no simple substance 'starch'—and the two major constituents of the granules—amylose and amylopectin are not entirely uniform substances. It is best to consider them as "macro-molecules"—in the sense of molecules having a generally constant composition-pattern repeated a considerable number of times; the number being constant only within a certain order.

The major constituents of starch, amylose and amylopectin, differ physically and structurally. Amylose is the simpler constituent occurring to the extent of about 20 per cent. in the granules; it has a molecular weight of the order $10^4 \rightarrow 6 \times 10^4$, and is purely carbohydrate in nature; amylopectin, the more abundant constituent, has a molecular weight of 5×10^5 to 10^6 and contains, in the case of tuber starches, combined phosphorus, in ester form. Amylose dissolves in water and gives elastic acetylamylose films; amylopectin swells up in hot water but does not dissolve—it confers the pasty quality on 'starch-paste' and its acetyl derivative is brittle. The action of β-amylase on amylose is to convert it completely to maltose; with amylopectin, the breakdown is partial, a mixture known as 'grenz-dextrin' being obtained in which about 40 per cent. of the amylopectin remains unchanged.

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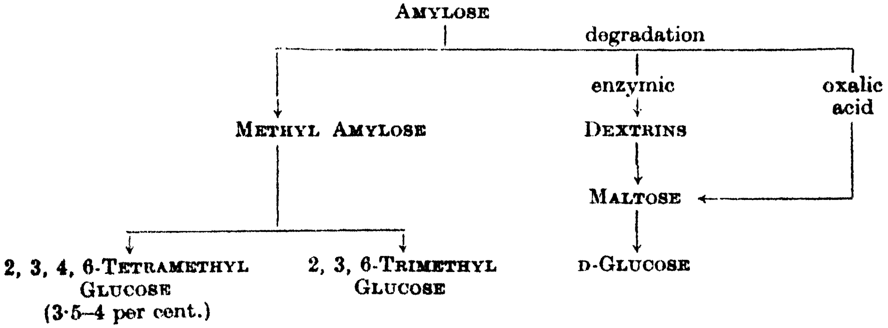
[1] See Appendix I.

There are several other constituents of starch—water forms part of the crystal lattice of amylose, since the crystalline structure revealed by X-ray analysis disappears on complete dehydration; in addition, there are small quantities of lecithins, and phosphoric acid compounds. Nearly all starches contain a small amount of amylose-phosphoric esters, and Posternak[1] has shown that whilst some of the phosphorus is extractable from starch in the form of glycerol-phosphoric acid, other portions are more firmly bound being released as D-glucose-6-phosphoric acid only on hydrolysis. Fatty acids are present in starch—in maize starch up to 0·6 per cent., in which palmitic, oleic and linoleic acids have been recognised.[2]

THE CONSTITUTION OF AMYLOSE AND AMYLOPECTIN

The empirical formula of starch, as determined by ultimate analysis, corresponds closely to $(C_6H_{10}O_5 . H_2O)_n$, from which it would appear that amylose is a glycosidic ether of a hexose sugar, of high molecular weight, with a molecule of water of crystallisation attached to each hexose unit. The decompositions of amylose shown in Table VIII indicate (*a*) that it is composed of maltose units, (*b*) that since the methylstarch gives a good yield of 2, 3, 6-trimethyl-*d*-glucose on hydrolysis, the orientation of glucose is pyranose, with links in the 1, 4-positions.

TABLE VIII



The question of the incidence of α- and/or β- glycosidic linkages in amylose has been settled by a consideration of the optical rotatory power, and the implications of Hudson's rule.[3] Amylose being soluble to a clear solution in formamide, its optical activity ($[\alpha]_D^{20} = +354°$) can be measured. The rotation of a substance composed of α-glucoside units will be given by

$$[\alpha]_D^{\beta\text{-maltose}} - [\alpha]_D^{\beta\text{-glucose}} = +403{\cdot}2° - 36° = 367°,$$

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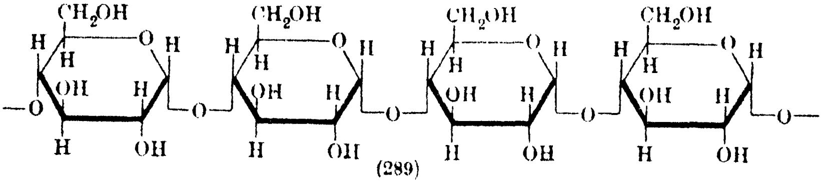
[1] Posternak, *H. Chim. Acta*, 1935, **18**, 1351.

[2] Taylor and Lehrmann, *J.A.C.S.*, 1926, **48**, 1739. Lehrmann, *ibid.*, 1932, **54**, 2527.

[3] Meyer, Hopff and Mark, *Ber.*, 1929, **62**, 1103.

whereas the figure for a β-glucoside structure would be much lower ; since the observed figure for amylose is so near the calculated figure there seems little doubt that very few β- linkages occur. The structure for amylose is therefore that of a succession of 1, 4- glucose moieties in chain formation as in (289). The question which immediately arises is " what happens at the end of the chain ? " Haworth and his co-workers [1] obtained some 2, 3, 4, 6-tetramethylglucose in the hydrolysis of fully methylated starch. The amount obtained indicated that the proportion of tetra- to tri-methylglucose was from 1 : 25 to 1 : 28. Haworth deduced from this that amylose starch consisted of a chain of 25–28 glucose units. This, however, does not agree with the molecular weight, especially in the case of the more complex starch, amylopectin. It has been shown that the experiments discussed above are somewhat misleading, as the methylstarch used is a mixture of methyl-amylose and methylamylopectin, the latter of which obscured the reactions of the former. Using a separated amylose of m.w. 45,000 (300 units) Meyer *et al.*[2] were able to show that the amount of tetramethylglucose obtained by the hydrolysis of methylamylose did not exceed 0·3 per cent., a figure which is in excellent agreement with the observed molecular weight. This leads to the conclusion that amylose is comprised of single chains of about 300 glucose moieties.


(289)

Since amylopectin has a larger molecular weight than amylose, and yields much more tetramethylglucose on hydrolysis of its methyl derivative it must have an arborescent structure. The Staudinger [3] structure (290) for amylopectin shows an arborescent molecule in which sub-units of 20–22 glucose moieties in the form of a straight chain are joined together in the manner indicated. Three hundred such moieties joined in 26–30 sub-units would constitute a ' molecule ' of amylopectin ; this ' molecule ' is not visualised as constant either as to size or arrangement. The type of structure associated with amylopectin molecule is shown in Fig. IV. Certain implications of this structure are capable of experimental verification ; thus reference to the structure (290) will reveal several glucose ' end-components ' (marked II) which will give rise to 2, 3, 4, 6-tetramethyl-D-glucose during hydrolysis of the methyl-amylopectin ; the majority of the D-glucose moieties (marked I) will give 2, 3, 6-trimethyl-D-glucose ; on the other hand, a few glucose fragments (marked III) can only give, on the hydrolysis of the methyl compound, a 2, 3-dimethyl-D-glucose. The isolation by Freudenberg [4] of the correct proportion of 2, 3-dimethylglucose from the hydrolysis products of fully methylated amylopectin affords at least a confirmation of the proposed structure.

Additional supporting evidence is forthcoming from consideration of the action of enzymes on amylose and amylopectin. Thus amylose is completely converted by β-amylase to maltose, but amylopectin is only partly so converted, the action of the enzyme being blocked at the branch (or IV) moiety. This means that the amylopectin molecule will be broken down as far as the broken line (- – – -) in Fig. IV. This, it has been suggested, is on account of

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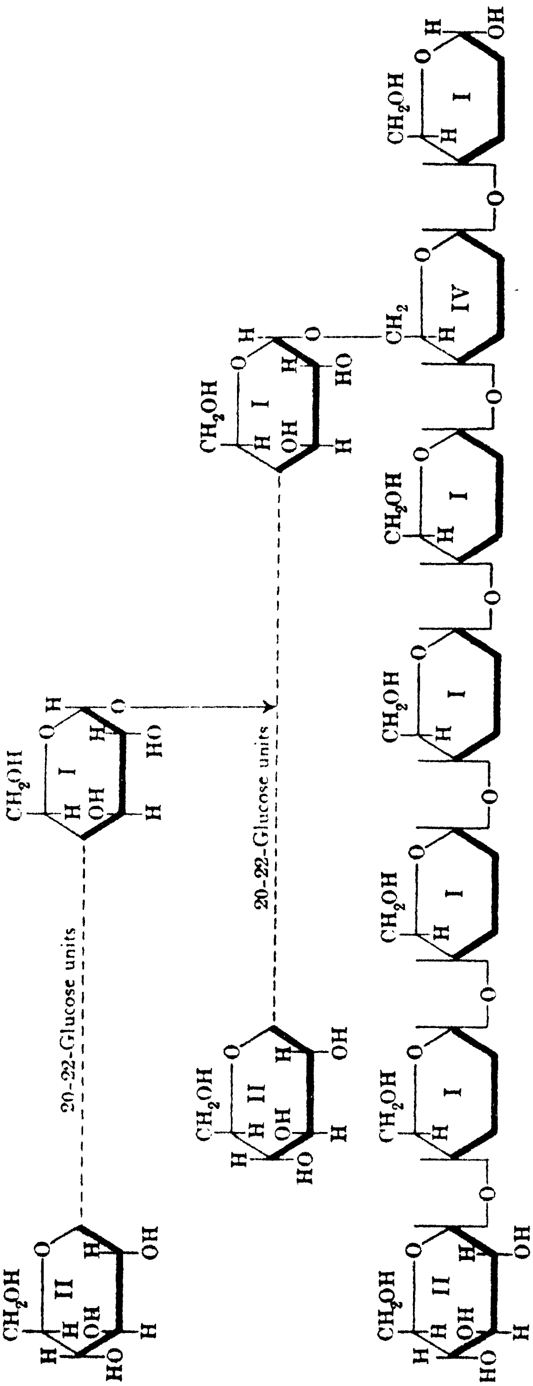
[1] Haworth, *et al.*, *J.C.S.*, 1928, 2681.
[2] Meyer *et al.*, *H. Ch. Acta.*, 1940, **23**, 865.
[3] Staudinger and Eilers, *Ber.*, 1936, **69B**, 819.
[4] Freudenberg and Boppel, *ibid.*, 1940, **73**, 609.



(290)

the β-6 glycosidic linkage at the junction, as shown in (291), which is unaffected by such enzymes as are capable of breaking down β-4-glycosides. On the other hand, such β-6 links are susceptible to attack by α-glucosidase and the residue is then again capable of further hydrolysis by β-amylase—up to the line (– · – · – · –) of Fig. IV ; and it is an experimental fact that alternate action of α- and β-glycoside enzymes will completely break down the molecule.[1]

THE AMYLOPECTIN STRUCTURE

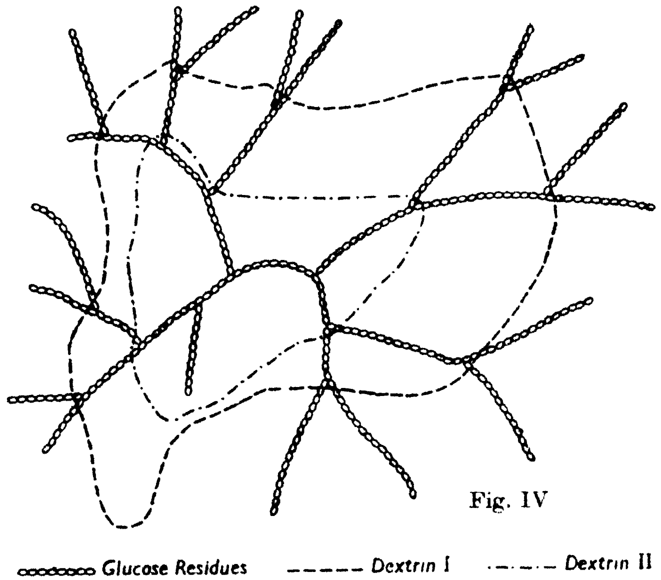
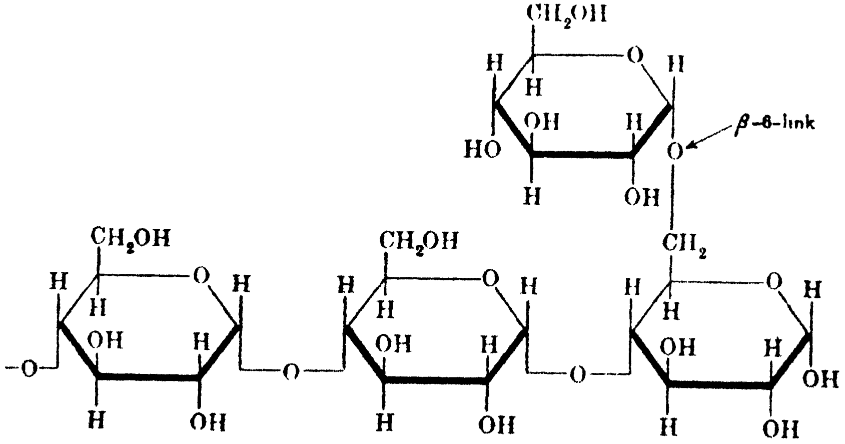


Fig. IV



(291)

Enzymatic Formation of Starch

The glucose ester of phosphoric acid, D-glucose-1-phosphate (292) is converted to starch when incubated in the presence of the enzyme phosphorylase[2] (e.g., that from potato-juice). The starch formed has a close resemblance to that portion of amylose which is less soluble in water. Thus, it gives a very intense blue colour with iodine, but is completely split by β-amylase. In these respects

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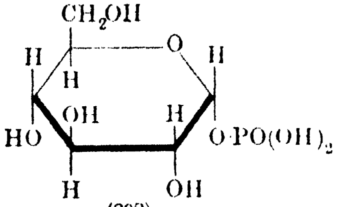
[1] Myrbäck, *Biochem. Z.*, 1938, **297**, 179 ; Hanes, *New Phytologist*, 1937, **36**, 189.

[2] Hanes, *Proc. Roy. Soc.*, 1940, **128B**, 421 : **129B**, 174.



(292)

it differs markedly from amylopectin, and resembles amylose, but differs from the latter in being less soluble in water and of a higher rotatory power. It is proper to mention, at this point, the fact that natural amylose appears to be a mixture of an extremely large number of amyloses of gradually increasing complexity and proportionate decrease in solubility in water. In view of the nature of starch and its relation to glucose and maltose, this is to be expected. The balanced equilibrium between glucose-phosphate and starch is of fundamental importance to plant economy, enabling the more complex carbohydrate to act as a readily available store of reserve material.

Some Reactions of Starch

It has already been implied in the foregoing sections that starch can be methylated. This may be done by the use of dimethyl sulphate in alkaline solution, and the methyl compounds extracted by taking advantage of their solubility in chloroform; the various fractionated amyloses give methyl compounds of increasing viscosity.

One of the most interesting properties of starch solutions in water is their ability to give blue colours or precipitates with iodine. This property is shown by other substances besides starch, including zinc chloride solutions of cellulose, colloidal lanthanum and praseodymium basic acetates,[1] and a number of aromatic derivatives such as sodium carbethoxyhydrindene.[2] Thus, it appears that the property is one comparable with adsorption, and it is assumed that the iodine is held by the secondary valencies of the starch molecule.

The action of heat and dilute acids on starch is to bring about a breakdown to 'dextrins'—a term used to cover the hexosans less in molecular size than amylose.

Lintner starch is one of the lesser altered amyloses obtained by allowing ordinary starch to stand in cold 7 per cent. hydrogen chloride solution for about 10 days. The breakdown of the starch has not proceeded so far that the product loses its power of giving a blue colour with iodine; on the other hand, it has become soluble in water. Meyer obtained an amylodextrin in crystalline spherites by continued treatment of starch with cold hydrochloric acid, but the dextrins themselves are obtained by heating starch to 110°, either alone or with a trace of nitric acid. The residue constitutes 'British Gum', and is a valuable stationery adhesive, and sizing agent for textiles.

The action of hot glycerol on starch leads to the formation of a soluble starch (Zulkowski-starch), which is probably the glyceryl glycoside of a polyhexosan. Schardinger[1] obtained crystalline substances from the degradation of starch by *Bacillus macerans*, they were termed

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[1] Krüger and Tschirch, *Ber.*, 1930, **63**, 826.
[2] Barger and Eaton, *J.C.S.*, 1924, **125**, 2407.

α-Tetramylose	$(C_6H_{10}O_5)_4$
β-Hexamylose	$(C_6H_{10}O_5)_6$
α-Octamylose	$(C_6H_{10}O_5)_8$.

They all appear to be polymeric maltose anhydrides, and represent the earliest stages in the building up of starch from maltose ; the ' α ' and ' β ' signs added to the names by Schardinger do not represent the type of glycosidic linkage which appears to be uniformly ' α '- throughout.

Some Other Starches

Animal starch or *glycogen* was isolated from liver by Claude Bernard[2] in 1857, and recognised by him as a substance capable of giving sugar by fermentation with an extract obtained from liver ; it was this phenomenon which led Bernard to choose the name ' glycogen ' for this substance. Glycogen does not normally form the granules so characteristic of vegetable starch, although in certain pathological conditions (e.g., diabetes) granules are found in the liver and muscle cells, presumably as the result of an abnormal effort to dispose of glucose. The conversion of glycogen $\rightleftharpoons$ glucose is very rapid, and is the basis of a mechanism by which the glucose content of the blood is maintained at a more or less constant level. Glycogen gives a brownish-violet colour with iodine, and appears to have a slight reducing action upon Fehling's solution.

As with vegetable amylose and amylopectin, the term ' glycogen ' does not represent a homogeneous individual substance, but rather a collection of substances, of gradually increasing complexity, but all built to the same pattern ; in general, the average molecular weight of the glycogen group is lower than that of the vegetable starches—about 40,000. Degradation with β-amylase only partially breaks down glycogen leaving a grenzdextrin similar to that from amylopectin ; methylated glycogen on hydrolysis gives the same 2, 3, 6-trimethylglucose, as does amylopectin, together with 2, 3, 4, 6-tetramethyl and 2, 3-dimethylglucose in equal proportions, amounting in all to 5–6 per cent. of the glucose units present. The most interesting work of Meyer and Fuld[3] has thrown much light on the structure of muscle-glycogen ; it has one end-group to each eleven glucose moieties (i.e., 9 per cent. of 2, 3, 4, 6-tetramethylglucose on hydrolysis of the methylglycogen) ; pure β-amylase removes about 50 per cent. of the molecule as maltose leaving a grenzdextrin ; this has now 18 per cent. of end-groups (i.e., one to each 5 or 6 glucose moieties).

From the evidence, it appears that glycogen and amylopectin have very similar structures, both are branched and built up of glucose moieties, part of which are joined by α-1, 4-glycoside links and part by α-1, 6 links. The difference between them lies in the fact that in glycogen both the outer units before the branch, and the inner units are much shorter than in amylopectin, being about 5 and 3 units respectively, whereas the outer units of amylopectin are 18–20 glucose units in length, and the inner chains 8–9 units.

A galactose polysaccharide has been isolated from the eggs of snails, and appears to be similar in nature to glycogen, but composed of galactose units ; it has, therefore, been called ' galactogen '. Although both di- and tetramethylgalactose have been isolated from the cleavage of its methyl derivative, its structure is not known with certainty.[4]

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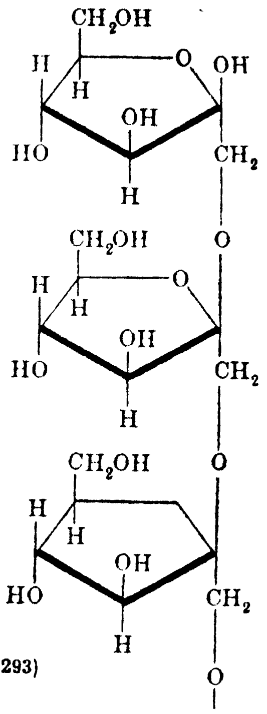
[1] Schardinger, *Zeit. Nahr. Genussm.*, 1903, **6**, 865.
[2] Bernard, *Jahresberichte*, 1857, 552.
[3] Meyer and Fuld, *Helv. Chim. Acta*, 1941, **24**, 375.
[4] Schlubach and Loop, *Ann.*, 1937, **532**, 228.

POLYFRUCTOSANS

The commonest polyfructosan is inulin, found in the tubers of the *Compositæ*; dahlia tubers are often used as a source of the crude starch, which may be extracted by grinding up the tubers with water, adding a little lime and boiling. The filtered extract is frozen; on thawing inulin is filtered off. Inulin was discovered by Valentine Rose in 1804 in elecampane root, and was soon recognised as distinct from ordinary starch in that it gives D-fructose on hydrolysis. It is insoluble in cold water, but even after much purification still shows a reducing tendency. Like D-fructose it is lævorotatory $[\alpha]_D^{20} - 40°$. Haworth and his colleagues[1] have submitted methylinulin to hydrolysis, and have isolated 3, 4, 6-trimethylfructofuranose, together with 3·7 per cent. of the corresponding 1, 3, 4, 6-tetramethyl derivative. The simplest interpretation of this data is that inulin consists of a chain of thirty fructofuranose units; the absence of dimethyl derivatives indicates an unbranched chain (293), and the conception of a thirty unit chain accords with the molecular weight figure of 5000 obtained by Drew and Haworth[2] from considerations of lowering of the freezing point. Not all polyfructosans are composed of units joined through the 1, 2-links; phlein, a polysaccharide from *Phleum pratense*, a kind of grass, has been shown to have 2, 6-glycoside links;[3] further details of its structure are obscure, but it must be composed of chains with configuration shown in (294).



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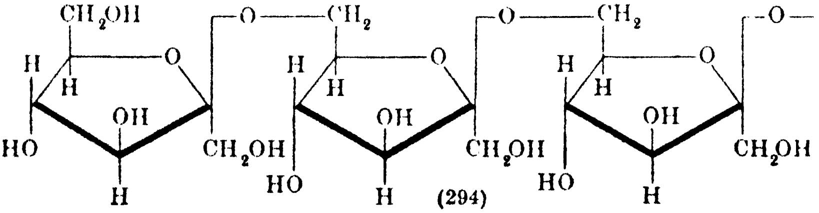

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CELLULOSE

Cellulose, and its related substances the hemicelluloses and pectins, are the main structural units of the vegetable system, and constitute the bulk of nearly all plant structures. The presence of cellulose in animal structures is rare, although the closely related tunicin is found in the Tunicate fish; bacteria are capable of building up specific polysaccharides some of which closely resemble the smaller cellulose structural aggregates; they are discussed on page 837. Cotton fibres, flax, hemp and wood are all materials consisting largely of cellulose, and from which it may be obtained.

The degradation of cellulose into simpler bodies follows out much the same plan as is observed with the starches, and the following stages are recognisable. In the first place, when cellulose is boiled with dilute acid a change takes place in the nature of the molecule and hydrocellulose is obtained. This has lost the fibre-strength associated with cellulose itself, and may be rubbed to a fine powder. The precise nature of the change is not clear, but it is very probable that the process is one of opening some of the glycoside links with consequent shortening of the chain; this would entail the addition of water, so that the term ‘hydrocellulose’ is correct. The gradual progression of cellulose to hydrocellulose can be followed by the decrease in viscosity of solutions of the product in Schweitzer's reagent (a cuprammonium solution). More drastic treatment, such as the solution of cellulose in concentrated acid, followed by precipitation on crushed ice leads to a white powder which has been more profoundly altered than has hydrocellulose. It is called ‘amyloid’ because it resembles amylose in giving a blue colour with starch; it has considerable reducing power towards Fehling's solution,[1] and X-ray examination reveals the same structure as that of mercerised cellulose.

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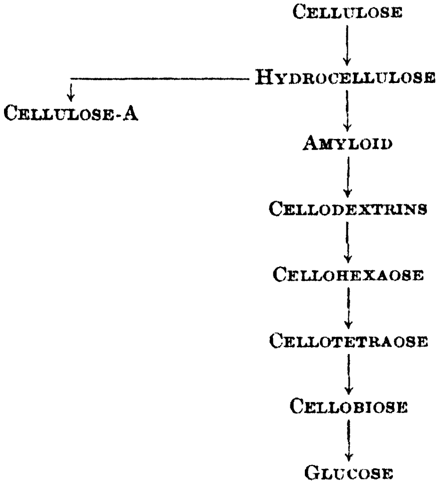
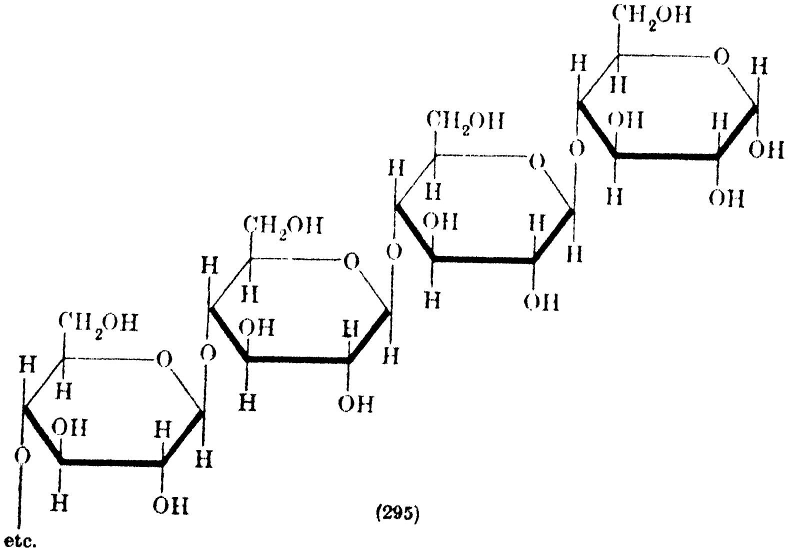
[1] Haworth, Hirst and Percival, *J.C.S.*, 1932, 2384.
[2] Drew and Haworth, *ibid.*, 1928, 2670.
[3] Schlubach and Sinh, *Ann.*, 1940, **544**, 10.





(295)

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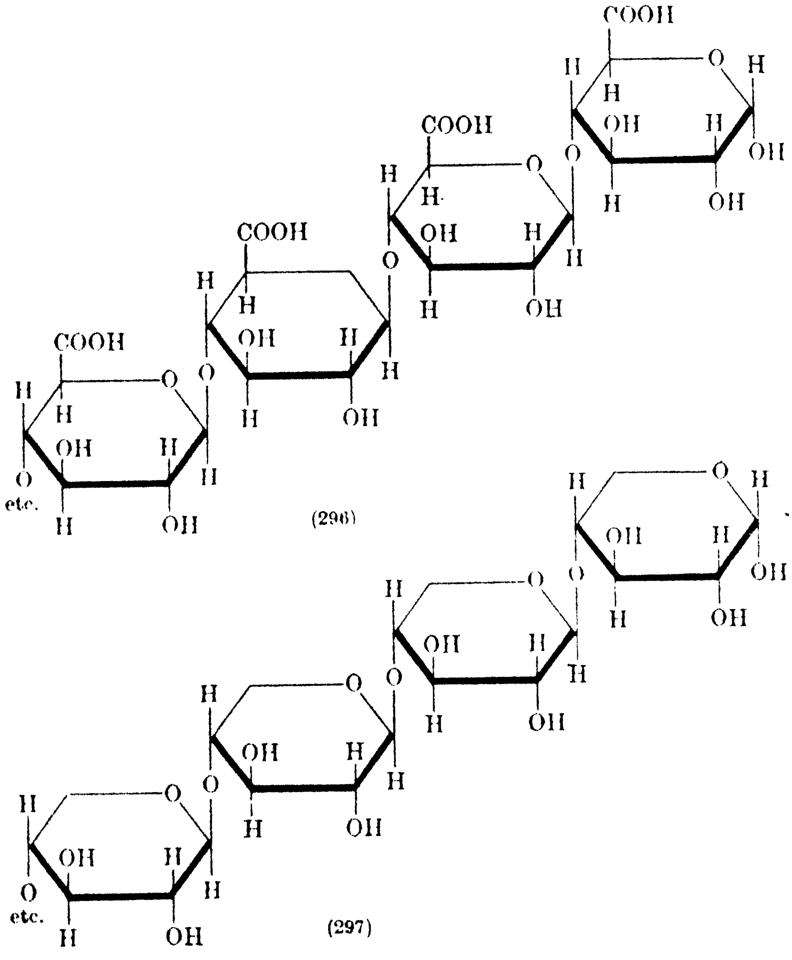
[1] Ekenstam, *Ber.*, 1936, 69, 549, 553.

If the solution in sulphuric acid referred to in the previous paragraph be allowed to stand for some time, further degradation of the material takes place and on precipitation a mixture of oligosaccharides is obtained to which the term 'cellodextrin' has been applied. Cellodextrins are not usually larger than thirty glucose units,[1] and the smaller members of the group are frequently crystalline. Further degradation gives cellohexaose, cellotetraose, and cellobiose, the latter having been synthesised (see p. 817). This degradation, through slow stages, may be accomplished rapidly and in one stage by the controlled use of sulphuric acid. This was demonstrated by Monier-Williams,[2] who obtained a yield of over 90 per cent. of crystalline glucose from cellulose and sulphuric acid.



(296)

(297)

It would appear, therefore, that cellulose is an aggregate of glucose moieties linked as cellobiose units; the isolation of 2, 3, 6-trimethylglucopyranose (together with a little 2, 3, 4, 6-tetramethylglucose) from the hydrolysis of methylcellulose confirms this view and leads to the adoption of the chain structure for cellulose, partially depicted in (295). This representation is to be taken only as a formalised expression of the structure, and not as a precise indication of arrangement. The more precise arrangement of the cellulose units in the fibre has been the subject of much investigation through the medium of X-ray analysis. The X-ray diagram shows that the fibres of natural cellulose consist of bundles of cellulose chains ; these may be linked chemically by transverse bonds due to the secondary valencies ; the observed fact [1] that a certain percentage of the hydroxyl groups of natural cellulose obstinately refuse methylation, indicate that such groups probably exercise a special function, the precise nature of which is not apparent. The X-ray diagram also reveals that the 'cross-bonds' are relatively few, and sparsely distributed throughout the fibres. The part played by the 'minority constituents' of cellulose may have some relation to the transverse binding. So far, nothing has been said about the minority constituents of cellulose, but it must be pointed out that the term 'cellulose', if taken to cover the aggregates of β-glucose chains solely, cannot accurately be applied to natural fibres. These always—no matter how carefully purified—contain the poly-β-glucuronic acid (296) and the xylan (297). Whether or not the poly-β-glucuronic acid is formed by the oxidation of the 6-group of cellulose is not clear ; nor yet whether xylan is formed by decarboxylation of the glucuronic acid.

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[1] Meyer and Mark, *Ber.*, 1928, **61**, 2432.

[2] Monier-Williams, *J.C.S.*, 1921, **119**, 803.

General consensus of opinion is that short glucuronic acid and xylan fragments occur at the edges of the micellar bundles. Thus, a formal picture of a cellulose fibre would involve chains of 200–300 glucose units bound together in bundles of 6–10 chains ; this unit is referred to as the 'micelle'.[2] Near the ends of the micelle—which is shown by X-ray measurements to be about 600 Å. long and 50 Å. in diameter [3]—some xylan and glucuronic units are to be found. The arrangement of the micelles in native cellulose depends largely on the type and function of the tissues examined, in the fibrils of bast fibre, for example, the micelles appear to be arranged parallel to one another lengthwise round a central cylindrical cavity ; in parenchyma cell-walls, where no axis of orientation is observable, they are in laminate form, but unorientated ; on the other hand, in cotton fibres the micelles are arranged at an angle of about 30° to the central axis ('screw' formation) ; in palm (e.g., coir fibres) the angle is as high as 45°. Such fibres are elastic, decreasing in diameter and sharpening in pitch as the load is increased.

SOME REACTIONS OF CELLULOSE

One of the most important properties of cellulose is its affinity for substantive dyes ; when cellulose fibres are placed in a solution of a dye—such as a Direct Cotton Red—the dye is concentrated and held by the hydroxyl groups at the internal intra-micellular interfaces.[4] This property is discussed in greater detail in Chapter XV, Vol. II.

Caustic soda has a profound effect on cellulose ; it is the basis of the process of mercerisation by which a glossy finish is imparted to cotton goods. It appears that the rough outer irregular micelles are partially liquefied by the action of the alkali, leading, on washing out, to the formation of a translucent, even and smooth outer coating. The alkali-cellulose combines with carbon disulphide to give a cellulose xanthate—the thick solution being used in the manufacture of regenerated cellulose threads—the so-called 'artificial' silk.

Passing reference has already been made to the solubility of cellulose in cuprammonium; the viscosity of the cuprammonium solution under standardised conditions being a measure of the 'strength' of the cellulose used; the cuprammonium solutions of cellulose can give regenerated cellulose fibres by forcing through dies into faintly acid baths—this giving the 'cuprammonium silk'. Cuprammonium solution may be prepared by exposing copper foil submerged in concentrated ammonia solution to the action of oxygen, and is essentially an ammoniacal copper oxide. The copper appears to form a complex

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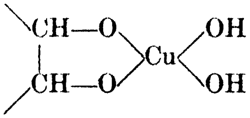
[1] Karrer and Escher, *Helv. Chim. Acta*, 1936, **19**, 1192.

[2] Nägeli, "Ostwald's Klassiker", 1928, **227**, Leipsic.

[3] Mark and Meyer, *Z. Physik. Chem.*, 1929, **2B**, 115 (*cf. Ber.*, 1931, **64**, 408).

[4] Hosemann, *Z. Physik.*, 1939, **114**, 133.



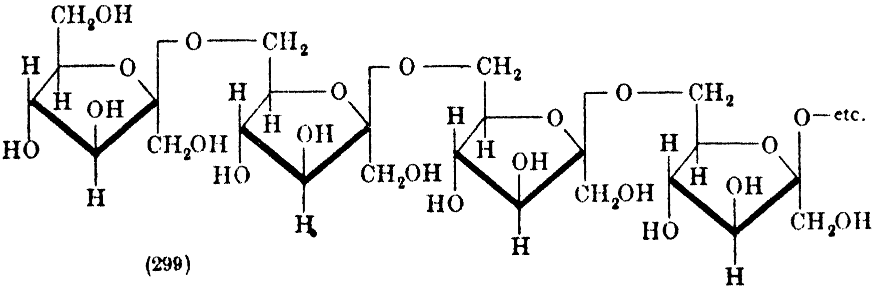
(298)

with the intra-micellular hydroxyl groups, probably of the type indicated by the formula (298). The formation is carried to such an extent that transverse intramicellular linkages break down and the cellulose goes into solution. The size of the micelle/copper particles in the viscous solution will depend on the size of the original micelles and their integrity; thus the relation between the viscosity of the cuprammonium solution and the 'strength' of the cellulose is virtually an expression of the micelle integrity.

The esters of cellulose have been discussed in Chapter VIII, and although full consideration of the regenerated cellulose fibres is deferred to Chapter IX, Vol. II, it may be remarked here that there is evidence of a micellular structure in regenerated cellulose, and also of orientation parallel to the fibre-axis.

BACTERIAL POLYSACCHARIDES

When *Acetobacter xylinum* is grown on media containing glucose it forms a bacterial cellulose, the structure of which is unknown, but which has a high molecular weight, as evidenced by the viscosity of its cuprammonium solution.[1] Such substances form the skeletal envelopes of the lower organisms, and it is surprising to find that the configuration of the polysaccharide has little or no direct relation to the structure of the hexose upon which it lives. Thus, *B. mesentericus* produces a fructosan (299) from glucose; this has been subjected to methylation and degradation by Haworth and his colleagues,[2] who isolated



(299)

1, 3, 4-trimethylfructofuranose with a little 1, 3, 4, 6-tetramethylfructofuranose. Other bacterial and fungal polysaccharides have been similarly investigated, some of the more important results being summarised in Table IX.

[1] Fikentscher, *Cellulosechemie*, 1932, **13**, 58.

[2] Challinor, Haworth and Hirst, *J.C.S.*, 1934, 676.

TABLE IX.

Organism	Name of polysaccharide	Type of unit	Type of linkage	References and comments
B. Mesentericus	Fructosan	Fructofuranose	β-2, 6-	
Yeast	Glucosan	Glucopyranose	1, 3	Skeletal substance Zechmeister and Toth, *Biochem. Z.*, 1934, **270,** 309
Betacoccus arabinosaceous (Leuconostoc dextranicum)	Dextran	Glucopyranose	α-1, 6	An 'iso-maltose' polymer Peat *et al.*, *J.C.S.*, 1939, 581 *J. Exptl. Med.*, 1925, **42,** 727
Pneumococcus I	—	Galacturonic acid + an amino-sugar + acetyl groups		
Pneumococcus II	Glucosan	*d*-Glucose		
Pneumococcus III	Cellobiuronic acid polymer	Aldobionic acid (Glucuronic acid/glucose)		Goebel *et al.*, *J. Biol. Chem.*, 1926, **70,** 613; 1927, **74,** 613; 1935, **110,** 301; 1938, **125,** 195
B. Pneumoniæ * **(Friedlander)**	—	Glucose + an aldobionic acid		
V. Cholera (W. 880)	Cholera polysaccharide	Galactose, arabinose + an aldobionic acid		Goebel *et al.*, *J. Exptl. Med.*, 1925, **42,** 701; 1927, **46,** 601
Tubercle bacilli	Tuberculosaccharides	D-Mannopyranose, D-arabofuranose + amino sugar units		Laidlaw *et al.*, *B. J. Exp. Path.*, 1925, **6,** 197. Chargaff *et al.*, *J. Biol. Chem.*, 1936, **112,** 393. Haworth, Kent and Stacey, *J.C.S.*, 1948, 1211
B. Lactis	Fructosan	D-Fructofuranose		From sucrose only Carruthers and Cooper, *Biochem. J.*, 1935, **29,** 2267
Penicillium varians	Varianose	D-Glucopyranose D-Idose D-Galactose	1, 4	Haworth, Raistrick and Stacey, *Biochem. J.*, 1935, **29,** 2668
Penicillium carlesii	{Galactocarolose Mannocarolose	D-Galactose D-Mannose	1, 5 α-1, 6	Haworth, Raistrick and Stacey, *Biochem. J.*, 1937, **31,** 640. Ditto. *Ibid.*
Penicillium luteum (Z.)	Luteic acid	Malonic acid + 80 D-Glucopyranose units	β-1, 6	*Biochem. J.*, 1939, **33,** 272

*** Each of the three types of Friedlander's bacillus yields a different polysaccharide which appears to be a permutation of *d*-glucopyranose and aldobionic units.**

These substances have been described as immuno-polysaccharides, since they are for the most part soluble substances capable of demonstrating some, at least, of the immunological specificity associated with the organisms themselves. Indeed, some of the polysaccharides can confer active immunity,[1] but many of them do not possess complete antigenic power, but are able to agglutinate immune sera prepared from the whole antigen ; the term ‘ hapten ’ is used of such partially active polysaccharides.

HEMICELLULOSES

Reference was made (p. 836) to the non-homogeneity of natural cellulose fibres, even after considerable purification ; there is present with cellulose, before such purification, three main types of allied substances, hemicelluloses, polyuronic acids and lignins. The proportion of these substances in cotton fibres is small, but in the case of timber, especially soft woods, it may rise to about 30 per cent. of the total. Considerable difficulty is experienced in separating the constituents sufficiently to obtain data on their constitution ; the ordinary methods of methylation and hydrolysis being, of course, inapplicable until comparatively pure starting materials are available.

PENTOSANS

Some mention has already been made of the presence of pentosans in oat-hulls and similar materials, in connexion with their breakdown to furfural. The commonest pentosan is xylan, although an araban, yielding L-arabinose on hydrolysis is also found in small quantities in wood.[2] The preparation of xylan is carried out by digesting the powdered material (e.g., oat-hulls) with caustic soda solution of 5 per cent. strength, filtering, and pouring the filtrate into alcohol. The precipitate so obtained is washed, digested with very dilute acid in aqueous alcohol and washed. To all external appearance it is an amorphous white powder. Its structure has been examined by Haworth and his colleagues.[3] On methylation xylan gives a dimethyl derivative which on hydrolysis yields 2, 3-dimethyl-D-xylose ; this confirms the 1, 4- structure of xylan set out in formula (297).

HEXOSANS

Cellulose itself is, of course, a glucosan in the sense that it is built up by duplication of D-glucose moieties, but there are, in addition, present in wood other and more soluble glucosans which can be extracted by dilute alkalies and which are split up by the sulphite used in the manufacture of sulphite pulp, thus accounting for the glucose in the waste liquor from this operation. The structure of these glucosans is, of course, analogous to that of cellulose, and differs only in the extent and pattern of the micellular arrangement. Whilst galactans have been detected—Mijama [4] found an insoluble galacto-araban in peanuts—they have not been extensively studied. On the other hand, the mannan from ivory nuts has been subjected to closer analysis, and appears to consist of mannose residues joined by β-1, 4 glycosidal links ; such a structure is shown in (300).

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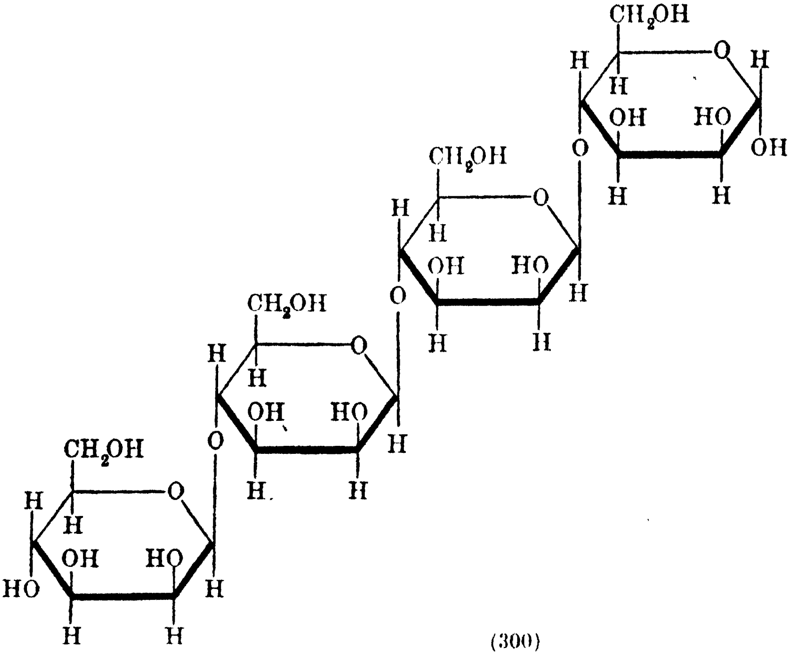
[1] Raistrick and Topley, *B. J. Exptl. Path.*, 1934, **15**, 113.

[2] Hägglund, “ Hölzchemie ” (2nd edn.), 1932, p. 122 (Leipsic).

[3] Hampton, Haworth and Hirst, *J.C.S.*, 1929, 1739.

[4] Mijama, *J. Dep. Ag. Kyush. Univ.*, 1935, **4**, 195.



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POLYURONIC ACIDS

Reference was made (p. 836) to the presence of glucuronic acid chains in cellulose. This is quite a general phenomenon, and it is thought that these acids are a genetic link between cellulose and xylan, being produced by oxidation of the projecting —CH_2OH groups of the former, and being decarboxylated by the plant to the latter. The Irish and Icelandic mosses (lichens) contain a hemicellulose, lichenin, which yields a solution in hot water which gelatinises on cooling. On methylation[1] it yields a derivative which is hydrolysed to 2, 3, 6-trimethylglucose and about 0·8 per cent. of 2, 3, 4, 6-tetramethylglucose. In view of Carter and Record's determination[2] of the molecular weight of lichenin as 20,000, this indicates an unbranched chain in 1, 4-glycosidal linkage which, from the optical rotation of lichenin acetate, appears to be of the β-type.

LIGNIN

The cellulose fibres of wood lie embedded in a mass of lignin which appears to act as a cement between the fibres as well. To obtain cellulose pulp for paper or rayon manufacture this lignin must be removed, an end which is achieved by heating the shredded wood with alkali or sulphite solutions under pressure. In this way the cellulose remains largely unattacked but the lignin goes into solution. Unfortunately the lignin is decomposed by this process so that little light is shed on its structure. The extraction of lignin from wood by concentrated acids or by solvents such as dioxan at high temperatures also degrades the lignin which appears to be a typical three-dimensional macro-molecule of indeterminate size. Hägglund[1] regards the molecule of lignin as of indefinite size, a network of primary valence chains acting as a bed and cement for the cellulose. The concept of molecule really disappears with macromolecules of this type.

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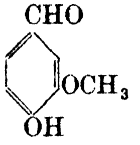
[1] Hess and Lauridsen, *Ber.*, 1940, **73**, 115.

[2] Carter and Record, *Chemistry and Industry*, 1936, 218.

Examination of the empirical formulæ of lignins obtained in different ways shows them not to be 'carbohydrates' in the strict sense of that term, the carbon content being greater and the oxygen less than the theoretical figure. In fact, there is little to relate the lignins to the polysaccharides except proximity of origin and macromolecular structure; they are essentially aromatic in character. The presence of methoxyl- groups in lignin was early established and served to divide the lignins into two main groups—the spruce-type lignins with a methoxyl content of 10–15 per cent., and the beech-type lignins with 19–21 per cent. methoxyl.

The breakdown products of lignins indicate their true character; cleavage with alkali yields eugenol, guaiacol, substituted guaiacols and protocatechuic acid; in the same way beech lignin yields similar products, together with gallic acid. When the sulphite liquor by which lignin is removed from cellulose is treated with hot alkali, vanillin (301) is produced in considerable yield—up to 10 per cent.; from beech lignin, syringa-aldehyde is also produced (302). The formation of such compounds has led to the suggestion that lignins are built up from a coniferyl alcohol unit (303), or in the case of beech lignin from a mixture of coniferyl alcohol and its methoxy derivative. The suggestion of such a formation was made originally by Klason[2] in 1897, and was subsequently widened in scope to include mixed coniferyl alcohol and coniferyl aldehyde units; it was also observed that all young plant tissue contained coniferin which could serve as a source of coniferyl alcohol.



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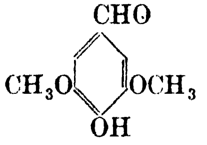

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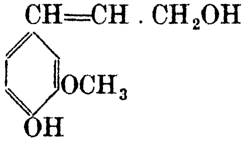
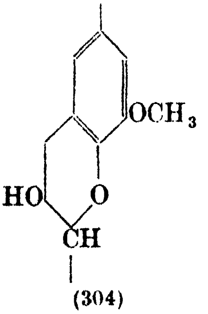


(303)

The mechanism of the linkage of such units is not properly understood; Freudenberg assumes that the unit (304) occurs five out of eight times in a spruce lignin, together with other units of which (305) is a prominent example leading to the gallic acid breakdown products, and is incapable of forming the chroman ring of (304); the isolation of vanillin-5-carboxylic acid (307) has led to the view that some, at any rate, of the units composing lignin are of the form (306);



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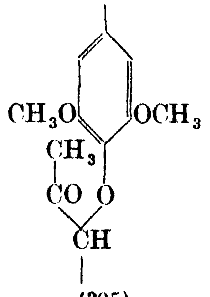

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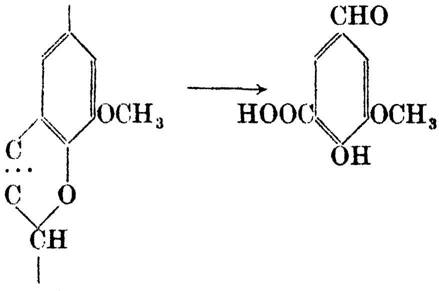

(306) (307)

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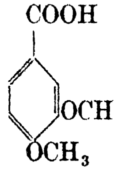
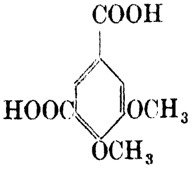
[1] Hägglund, "Holzchemie", *loc. cit.*

[2] Klason, *Svensk. Kem. Tidskr.*, 1897, **9**, 135.

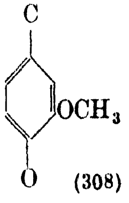
the isolation, too, of veratric and *iso*-hemipinic acids from the methylation of lignin (diazomethane) and hydrolysis of the methyl lignin, leads to the supposition that the plain 'veratryl' link (308) must also be present in lignin. A portion of lignin molecule on this hypothesis would have a structure such as (309), although condensation to form two- and three-dimensional units is also contemplated. A second view of the structure of lignin was put forward by Erdtman about 1933, in which he took exception to the ring-type (marked I, in 309) of Freudenberg's proposed structure, remarking that such a formation was uncommon in natural products, and should be associated with a partially active —CH_2 group. His alternative suggestion is a unit (310) in which the offending ring is replaced by a smaller ring similar to that found in a variety of structures such as egonol.[1]



Veratric acid



iso-Hemipinic acid



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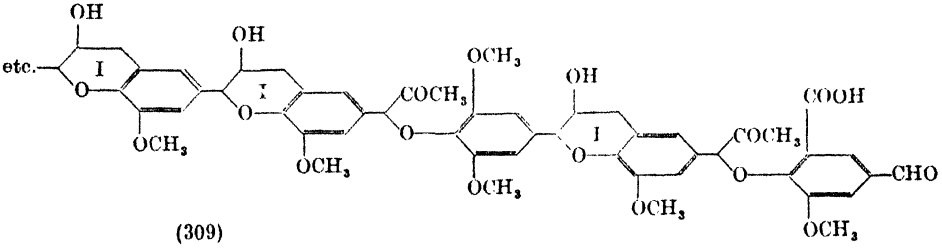

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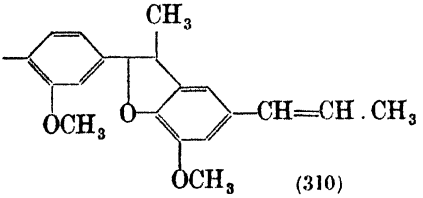

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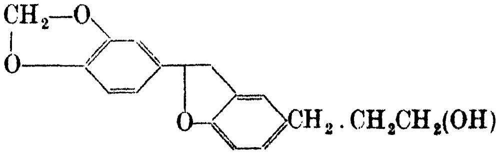

(311)

Hibbert has carried out a wide range of researches on lignin in Canada, the results of which are embodied in a series of over seventy papers. He does not, it appears, feel that the time is ripe for an authoritative statement on lignin structure, although his data confirms the Freudenberg suggestion that the basic unit of the lignin molecule is derived from phenylpropane; thus, he has obtained from spruce by the action of hydrogen chloride in ethanol the series of compounds illustrated in (312 to 315).

Hibbert also comments upon the similarity of the side-chain of these units to certain stages in the ascorbic acid ene-diol oxidase system of Szent-Gyorgy, and suggests that this may be of fundamental phytochemical significance.

Russell[2] not only claims that lignin has the structure (315c) but that he has synthesised a product identical with gymosperm (larch) lignin from vanillin monoacetate, which rearranges with anhydrous aluminium chloride to give 2-hydroxy-3-methoxy-5-formyl acetophenone (315*a*) which polymerises to the

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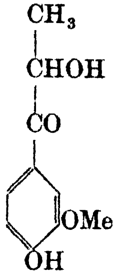
[1] Kawai and Sujiyama, *Ber.*, 1939, **72**, 369.

[2] Russell, *Chem. and Eng. News*, 1947, **25**, 2894.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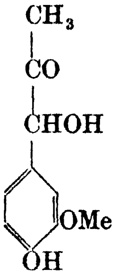
1-(3-methoxy-
4-hydroxyphenyl)
propanol-2, one-1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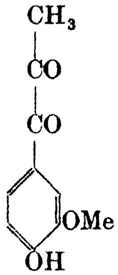
1-(3-methoxy-
4-hydroxyphenyl)
propanol-1, one-2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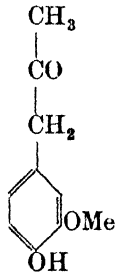
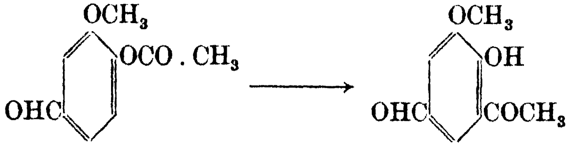
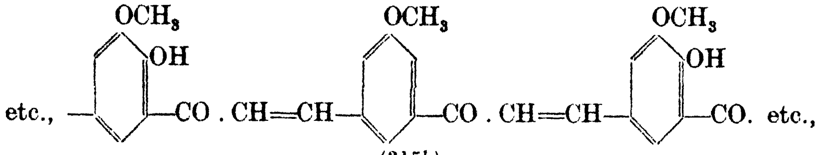
1-(3-methoxy-
4-hydroxyphenyl)
propandione-1, 2


(315)
(3-methoxy-
4-hydroxyphenyl)
propanone-2

structure (315*b*) by a Claisen condensation. The details of cyclisation to (315*c*) are not cited in the reference available.


(315*a*)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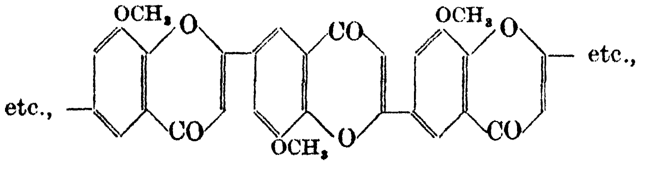

(315*c*)

PECTINS AND RELATED SUBSTANCES

There is no recognised logical system of nomenclature for this group of substances, most of which have a gelatinous nature and are physically ill-defined. The following divisions are based on the sources from which the substances are derived, rather than from any inherent properties which they possess :—

(1) *True pectins.*—Obtained from the cells of fruits and usually consisting of esters of pectic acid.

(2) *Fucopectins.*—Derived from seaweeds ; different varieties give different products, e.g., alginic acid from *Laminaria digitata* and Laminarin from *L. cloustroni* ; agar-pectin from agar seaweeds.

(3) *Gum-pectins.*—This class includes the mucilages from plant sources, and may be subdivided :—

(*a*) *Plant mucilages*, e.g. from *psyllium* or *orchidacæ* (e.g. salep-mannan).

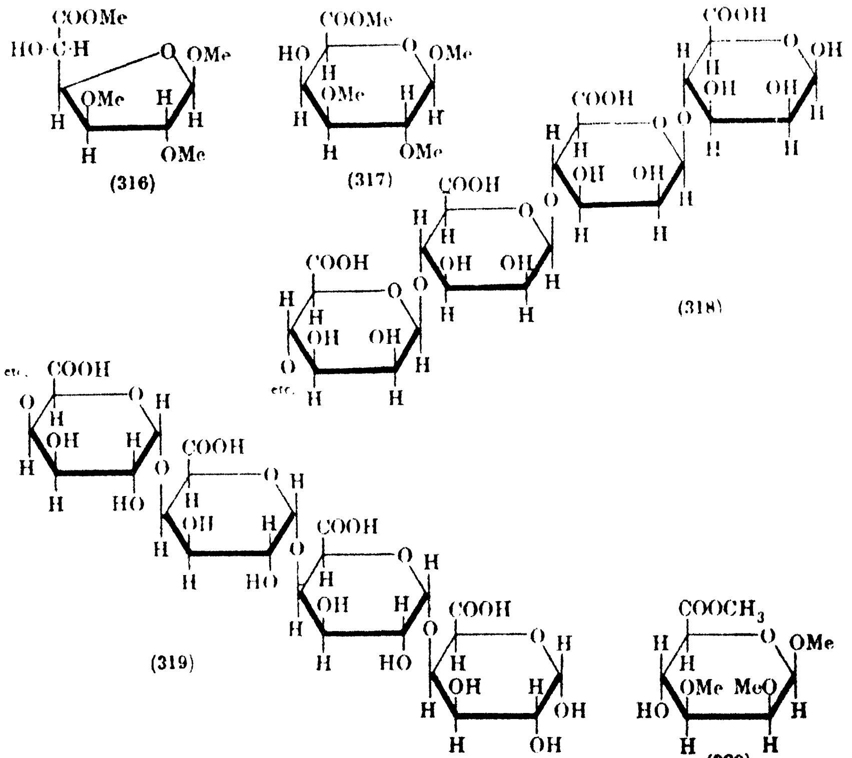
(*b*) *Yeast gum.*

(*c*) *Gum arabic.*

(*d*) Cherry, plum and damson gums ; citrus gums ; tragacanth.

All the members of this group are related by their physical properties and by the fact that on hydrolysis they give uronic acid or aldose units. They differ from starch and cellulose in two main respects (*a*) the presence of a preponderating amount of uronic acid residues, and (*b*) the absence of crystallite or fibre formation. Most form unorientated gums or jellies, the structure of which appears to be based on a random three-dimensional formation.

True pectins are obtained from apple, pear or citrus pomace after the expression of juice and oil. Hot dilute sulphuric acid dissolves the pectin from the pomace and the pectin itself may be precipitated from the solution by alcohol.



(316) (317) (318) (319) (320)

It is to be noted that pectin as a term is not a precise description, but covers a whole range of substances produced in this way ; by fractional precipitation or extraction, more, or less, soluble pectins may be obtained, whose solutions indicate by their viscosities a proportionately higher or lower molecular weight. The commercial fruit pectins (mainly citrus (lemon) or apple) are prepared from the more soluble or first extracts. There is little doubt that a change takes place during the extraction of pectin, and that the 'primitive' pectin existing in the plant cell tissues is broken down during the extraction ; Ehrlich[1] and his co-workers have shown that by repeated extractions, an araban can be obtained from pectins of high molecular weight.

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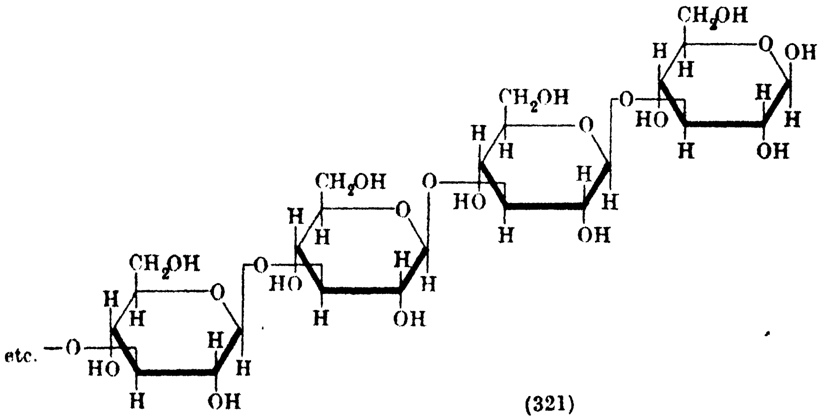
[1] Ehrlich *et al.*, *Biochem. Z.*, 1926, **168**, 263 ; 1926, **169**, 13 ; 1928, **203**, 343. *Ber.*, 1929, **62**, 1974.

The breakdown of pectins shows D-galactose, D-galacturonic acid and L-arabinose, a series exactly analogous to the D-glucose, D-glucuronic acid and D-xylose of the cellulose series. In addition, methyl alcohol is found as a product of hydrolysis of pectin ; the latter appears to be a methyl ester of pectic acid, the alcohol having esterified some of the carboxyl groups of the galacturonic acid units. It does not appear to be true, as thought by Ehrlich, that the arabinose, galactose and galacturonic acid units are built up into the same chain—it is far more probable that the three types of unit form three different chains, which themselves are interwoven in the primitive pectin. The polyuronide chains predominate and on methylation of pectin and hydrolysis the methyl ester of 2, 3-dimethylgalactofuro-uronoside (316) is obtained. This is not formed directly, but by a rearrangement of the galacto pyranuronoside (317) first formed. The chain structure of pectic acid is therefore that shown in (318), the units being arranged in α-1, 4 glycosidic formation.

On the other hand alginic acid, the acid of the fucopectin algin, has been shown to be constituted from mannose units in β-1, 4 glycosidic union (319). Algin occurs in seaweed (particularly *Laminaria digitata* together with fucosan, a polymeride of fucose moieties. Hirst and his colleagues [1] were successful in methylating alginic acid and hydrolysing the methyl derivative to 2, 3-dimethyl methyl-D-mannuride methyl ester (320). The chain of alginic acid (319) is, therefore, entirely analogous to that of cellulose. On the other hand, it appears that laminarin, an apparently similar fucopectin, possesses a β-1, 3 linkage. This fucopectin obtained from *Laminaria cloustoni*, gives on methylation a methyl derivative which may be hydrolysed almost exclusively to 2, 4, 6-trimethylglucose.[2] It is therefore not an uronide, but a glucoside and is linked at the —1, 1, 3 positions; its structure is, therefore, represented by (321). In the same way agar appears to be derived from the corresponding galactose compound (322), again linked in a β-1, 3 glycosidic chain. The problem, in the case of agar, is complicated by the fact that some of the galactose residues are esterified with sulphuric acid. Pirie [3] pointed out, also, that L-galactose was produced in about 6 per cent. yield by the hydrolysis of agar. This might have arisen from some adventitious racemisation of the D-galactose, but it became clear that this was not the case when methylated agar was shown to give a



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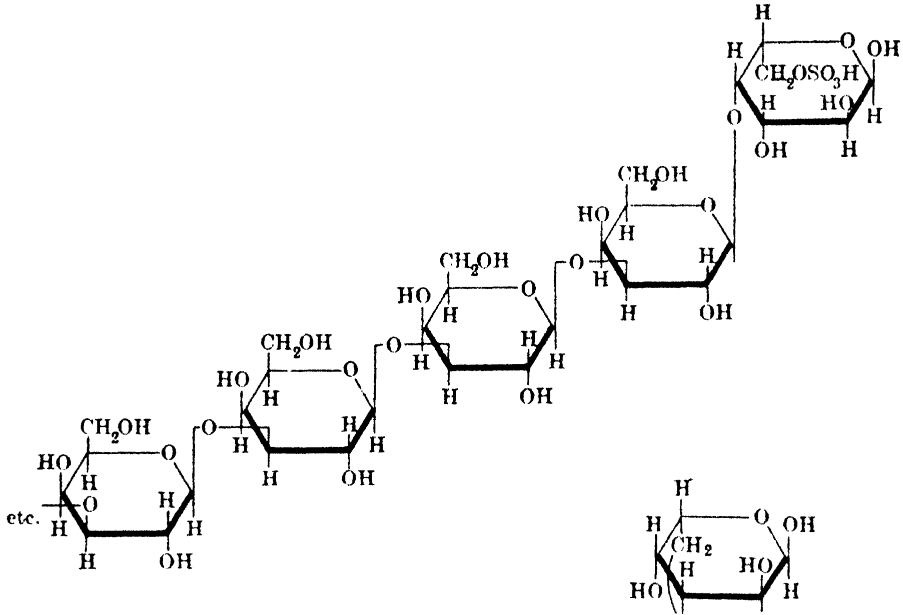
[1] Hirst, J. K. N. Jones and W. O. Jones, *J.C.S.*, 1939, 1880.
[2] Barry, *Sci. Proc. Roy. Dublin Soc.*, 1939, **61**, 1223.
[3] Pirie, *Biochem. J.*, 1936, **30**, 369.

similar percentage of anhydrodimethyl-L-galactose on hydrolysis. The anhydro-ring is in the 3, 6-position (322*a*); it was conjectured that such a ring was formed during the hydrolysis of the sulphuric ester group. Since only the 2-group of the L-galactose is methylated (the second methyl group being glycosidic) the substance must be methyl 2-methyl-3, 6-anhydro-L-galactoside. It is therefore an end component joined through the '4' position; this is depicted by the end-group in formula (322).



(322) (322*a*)

It cannot be said that the structure of the gum-pectins has yet been elucidated; tentative structures can only be suggested in the case of gum arabic. Gum arabic (the secretion of a species of acacia) is the salt of arabic acid and hydrolysis yields [1] a mixture of saccharide units :—

	Per cent.
Galacturonic acid	20
Galactose	30
Arabinose	34
Rhamnose	14

If the hydrolysis of arabic acid is carried out by boiling water, L-arabinose, L-rhamnose and a disaccharide (3-galactosido-L-arabinose) are split off and a fraction remains which is resistant to hydrolysis. The latter, on methylation, followed by hydrolysis of the methylated product yields :—

2, 3, 4-Trimethylgalactose (5 mols.)	*A*
2, 4-Dimethylgalactose (2 mols.)	*B*
2, 3, 4, 6-Tetramethylgalactose (1 mol.)	*C*
2, 3, 4-Trimethylglucuronic acid (3 mols.)	*D*

This would indicate a progressive chain of mixed 1, 3- and 1, 6-glycosidically-joined galactose moieties, with branch chains of comparatively short length joining the '6' positions of the main chain, through a galactose unit to a galacturonic end-group; the capital letters of the methylated fragments above

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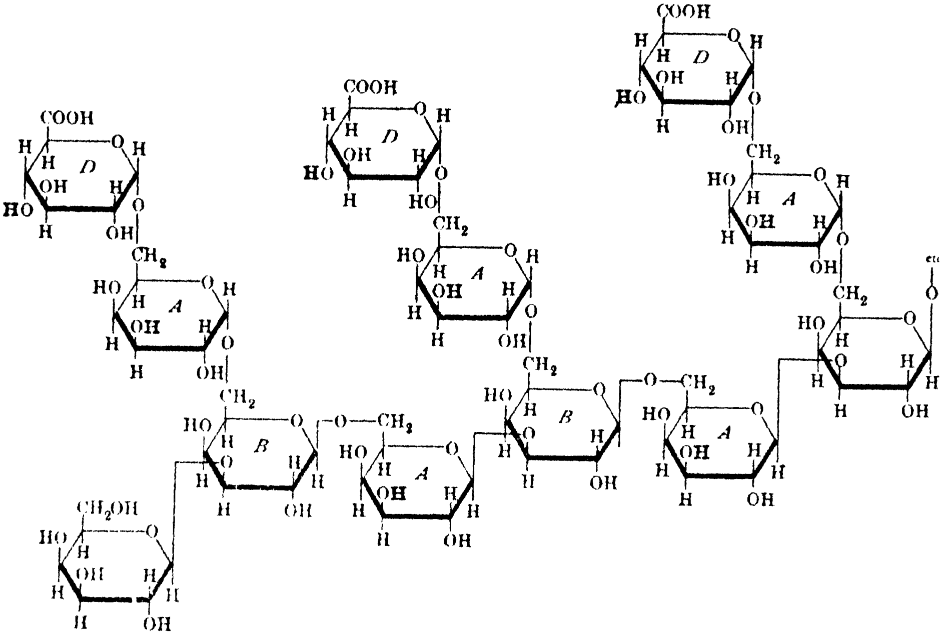
[1] Smith *et al.*, *J.C.S.*, 1939, **744**, 1724; 1940, **74**, 79 and 1035.

correspond to those in the centre of the rings in formula (323). It must, however, be repeated that this is a proximate structure for the unit of degraded arabic acid; the formula of the latter will, of necessity, include the arabinose, rhamnose, etc., residues split off in the preliminary hydrolysis.



(323) (glycosidic orientations arbitrary)

The situation of these additional groups is almost certainly in the '3' positions of the nuclei marked '*A*' in (323), and in the '4' positions of the glucuronic acid units. These positions are indicated in structure (323) by bold type '**H**'. The nature of the groups attached at these points is very uncertain; inasmuch as the amount of arabinose obtained during hydrolysis of arabic acid is roughly equal to the galactose formed, it would seem that each of the points of attachment in (323) will carry one arabinose moiety; since both 2, 5-dimethyl- and 2, 3, 5-trimethyl-L-arabofuranose are obtained from the hydrolysis of fully methylated arabic acid, it appears (*a*) that the arabinose residues are present in furanose ring form, and (*b*) that part of them are end-groups and part links in a chain; since 2, 3, 4-trimethylrhamnose is found also, it is probable that rhamnose constitutes an end-group.

Thus, it would appear that the formula (323) must be enriched by a rhamnose-arabinose disaccharide moiety at three points, with a simple arabinose moiety at five points; it is tempting to suggest that the former may be attached through the '4' positions of the '*D*' groups, and the latter through the '3' positions of the '*A*' groups.

Other gums have been subjected to an analysis of a similar character, in particular damson gum, which was investigated by Hirst and Jones.[1] The decomposition of this gum and its methyl derivative gave novel results, including the isolation of a 2-glycoside—an almost unique instance of such a component in the polysaccharide field. The details cannot be given here, but the reader is referred to Dr. Peat's excellent summary of the data on this and related problems (Appendix I to this chapter).

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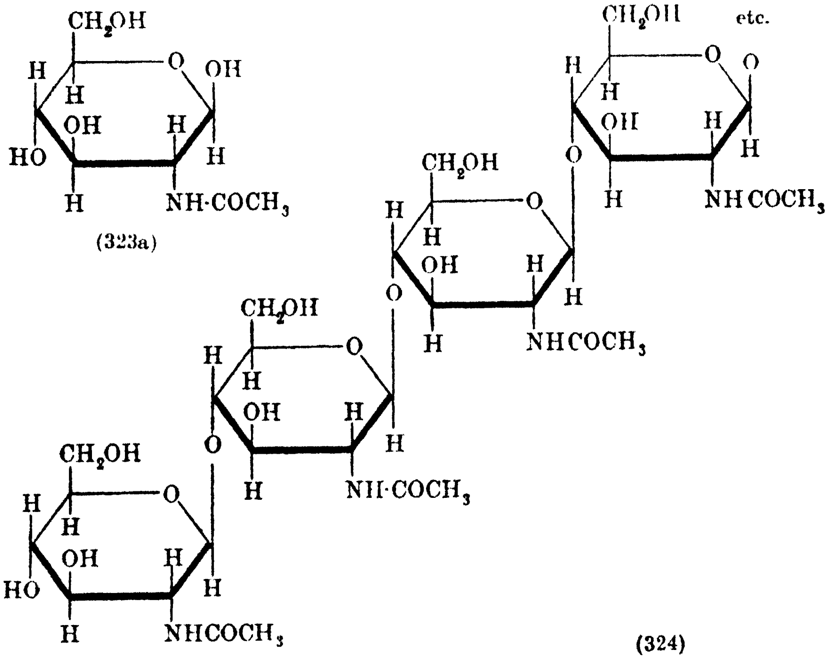
[1] Hirst and Jones, *J.C.S.*, 1938, 1174; 1939, 1482.

CHITIN AND RELATED COMPOUNDS

The claws, carapaces and skeletal material of molluscs, much of the quasi-skeletal material of anthropods and annelids, and the structural material of fungi, consists of chitin, a nitrogenous polysaccharide. In the structure of lower animal organisms and fungi, chitin plays a part of a supporting structure, similar to the function of cellulose in plants. When hydrolysed it yields glucosamine and acetic acid almost exclusively. The unit of chitin must, therefore, be 2-acetylaminoglucose (323a); confirmation of this has been obtained by various workers[1] who have determined the orientation of the groups in the hexoseamine (at first thought to be a mannose and not a glucose derivative). The β-nature of the glycosidal linkage was worked out by Zechmeister *et al.*,[2] and its nature as a 1, 4- link by Bergmann and his co-workers,[3] who isolated



(323a)

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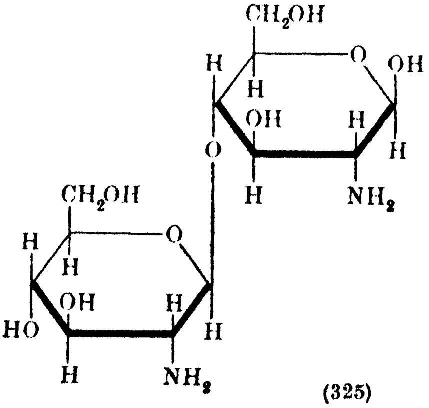

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[1] Haworth, Lake and Peat, *J.C.S.*, 1939, 271; Karrer and Mayer, *Helv. Chim. Acta*, 1937, **20**, 407.

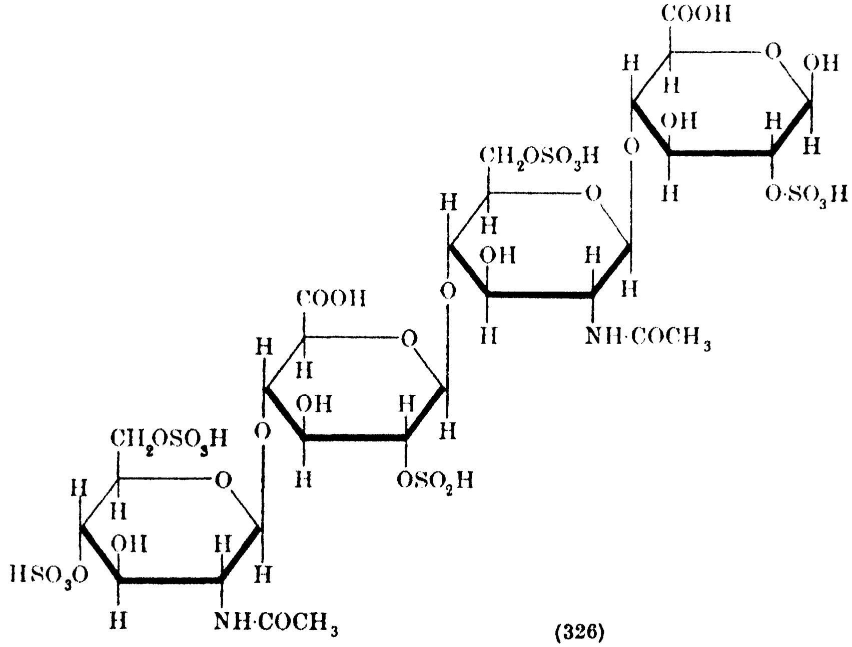
[2] Zechmeister *et al.*, *Ber.*, 1932, **65**, 1706; 1933, **66**, 522.

[3] Bergmann *et al.*, *ibid.*, 1931, **64**, 2436.

and characterised chitobiose, a disaccharide which bears the same relation to chitin as cellobiose to cellulose ; indeed, chitobiose may be regarded as cellobiose in which the 2, 2′-hydroxyl groups have been replaced by amino groups (325).

The X-ray analysis of chitin fits well with the structure set out in (324), and indicates that it has a micellar structure of chains in parallel orientation, similar to that of cellulose. Here again, it is legitimate to extend the analogy which exists between cellobiose and chitobiose, and to regard chitin in a general way as a 2_0^{∞} -acetylamino cellulose.

A closely related substance is the chondroitin sulphuric acid which may be extracted by N/2 caustic soda solution from shredded cartilage. This solution, clarified and precipitated by alcohol, yields a sodium salt of chondroitin sulphuric acid, which is probably one constituent unit in the complex structure of the proteins. If it is subject to bacterial hydrolysis (by *B. fluorescens non liquefaciens*),[1] it yields D-glucuronic acid, chondrosamine (D-galactosamine), D-glucosamine together with acetic and sulphuric acids. It must, therefore, be an assemblage of these units ; at the moment, little is known of the position and type of linkage binding them together. The main interest of this substance lies in its relation to *heparin*. Heparin was the name given by Howell and Holt in 1918 to a purified extract from liver which had the power in low concentrations (1 in 100,000) of preventing the coagulation of blood. Purified heparin, subjected to the exhaustive researches of Jorpes (see Appendix I) was shown to be a mucoitin polysulphuric ester consisting of two molecules of acetylglucosamine, two of glycuronic acid and five of sulphuric acid. In a very large number of reactions and properties heparin resembles chondroitin sulphuric acid, but differs in physiological properties. Bergström,[2] however, showed that a moderate anti-coagulant activity could be conferred on chondroitin sulphuric acid by treatment with chlorosulphonic acid which would



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[1] Neuberg and Cahill, *Atti. acad. Lincei*, 1935 (6), **22**, 149.

[2] Bergström, *Naturwiss*, 1935, **23**, 196 ; *Zeit. physiol. Chem.*, 1936, **268**, 163.

make it appear that heparin is a more highly sulphated member of the same group. Elmer and his co-workers [1] obtained a polysaccharide sulphuric ester from agar of comparable activity to that of heparin. Heparin must therefore have a structure somewhat similar to that shown in (326) in which, however, the arrangement of β-links and acid groups is arbitrary.

Such esters constitute the prosthetic groups of the mucoproteins a further discussion of which will be found in Vol. II, Chapter IX.

APPENDIX I

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[1] Elmer, Broser and Bürgel, *Z. physiol. Chem.*, 1937, **246**, 244.

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APPENDIX II

GLYCOSIDES

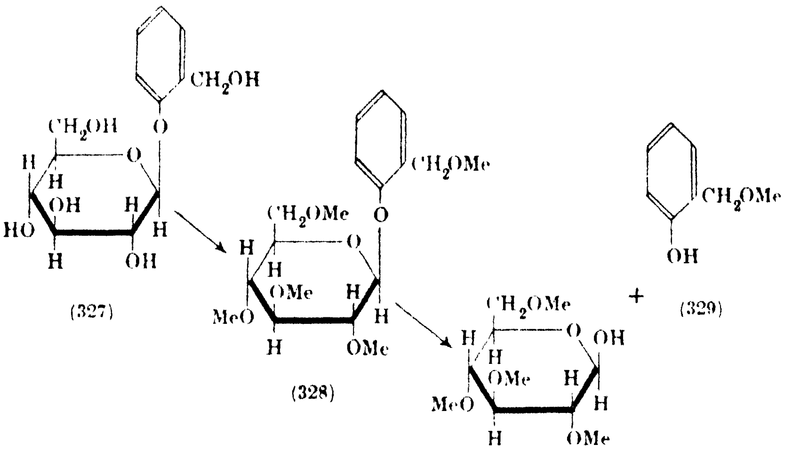
In the main portion of this chapter considerable reference has been made to glycosides, especially in connexion with the sugar di- and tri-saccharides, and with the linking of units in the polysaccharides and polyuronides. The term 'glucoside', it should be mentioned, is restricted to those substances in which glucose itself constitutes one moiety; 'glycoside' is a general term covering any substance in which one moiety is a sugar molecule. The nature of the second portion of a glycoside is used to divide the whole family into two groups; glycosides in which both moieties are sugar molecules are called 'holosides'; those in which one portion is derived from a non-sugar structure are named 'heterosides'. Thus, all the sugars and polysaccharides discussed in the earlier portions of this chapter are holosides; this appendix deals with the heterosides. Attempts have been made to classify the heterosides into families, but with no great success, for whilst it is possible to make broad distinctions—such as the well-recognised groups of cyanogenetic glycosides, and the cardiac glycosides, many, such as indican, do not fall easily into such a classification. On the other hand, classification according to the nature of the sugar moiety brings the hetero-units, known as 'aglycones', into unsuitable groups. It is probably best to divide the heteroside family into broad groups thus:—

Group I.	Cyanogenetic glycosides.
Group II.	Steroid glycosides, including the cardiac glycosides.
Group III.	Simple aryl glycosides.
Group IV.	Chroman and flavone or plant-pigment glycosides.
Group V.	Tannins.

It will be clear from the divisions indicated above, which by no means exhausts the scope of the heteroside family, that the subject-matter of this appendix will largely be confined to (*a*) the nature of the link between the sugar and aglycone, (*b*) the nature and configuration of the sugar moiety; any detailed consideration of the aglycone will be referred to the appropriate section into which it falls by virtue of its chemical type.

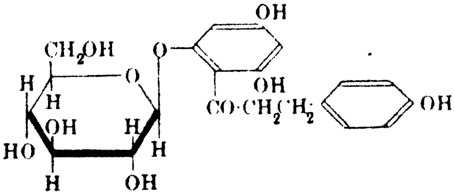
As a typical example of a simple aryl heteroside, salicin may be considered; it has been extracted from willow and poplar barks on which it confers the therapeutic properties which have led to the use of such barks as febrifuges, from the earliest times. The extraction of salicin from the bark led to its introduction into medicine about seventy years ago.

When hydrolysed by dilute acids, salicin yields *o*-hydroxybenzyl alcohol (saligenin) and D-glucose; on methylation salicin gives a pentamethylsalicin (328) which on hydrolysis yields *o*-hydroxybenzylmethyl ether (329) and 2, 3, 4, 6-tetramethylglucose. This methylation and decomposition were carried out by Irvine and Rose [1] in 1906, but the precise structure of the methyl sugar was not determined until much later. The structure of salicin is therefore to be visualised as (327). It will be noted that the glycosidal link is β- in character, a fact



which is established by its sensitivity to emulsin. Numerous glycosides are known which produce a hydroxy-aryl derivative on hydrolysis; the chief of these are mentioned in Table X.

One or two in Table X call for comment; phloridzin is a rather more complex structure than some of the others (330). It is used in biochemical laboratories



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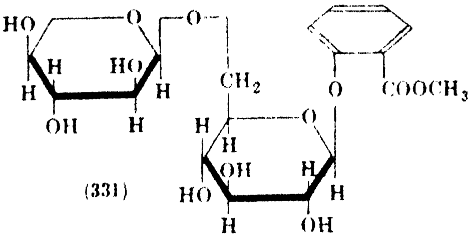

to produce severe glycosuria in experimental animals (a species of artificial diabetes); alloxan is capable of inducing a similar effect. Gaultherin (331) is also an unusual glycoside of this group, giving the rare disaccharide primeverose on hydrolysis. The breakdown and hydrolysis of coniferin (332) is of unusual interest, and links this glycoside with the lignins. On chromic oxidation it gives glucovanillin (333), and this on hydrolysis yields glucose and vanillin. This process was actually used for making vanillin 70 years ago; the product

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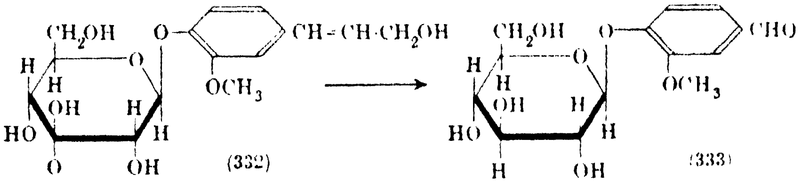
[1] Irvine and Rose, *J.C.S.*, 1906, 89, 814.

TABLE X

Name	Source	Sugar	Aglycone	M.P. of aglycone
Arbutin	*Ericaceae*, generally bearberry and pear	D-Glucose	Hydroquinone	170°
Methyl arbutin	Bearberry and pear	D-Glucose	Methylhydroquinone	
Salicin	Willow and poplar	D-Glucose	Salicyl alcohol	82°
Populin	Poplar bark	6-Benzoyl glucose	Salicyl alcohol	82°
Phloridzin	Root-bark of Pyrus and prunus	D-Glucose	Phloretin (Phloretyl phloroglucinol)	
Glycophyllin	*Smilax glycophylla*	Rhamnose	Phloretin	
Gein	Common avens	Vicianose	Eugenol	
Melilotin	*Melilotus* species	D-Glucose	*o*-Coumaric acid	
Aesculin	*Aesculus Hippocastanum* (horse chestnut)	D-Glucose	Aesculetin (6, 7-dihydroxycoumarin)	The coumarin aglycones 268°
Daphnin	*Daphne* species	D-Glucose	Daphnetin (7, 8-dihydroxycoumarin)	256°
Fraxin	*Fraxinus* species	D-Glucose	Fraxetin (6-methoxy-7, 8-dihydroxy-coumarin)	227–228°
Coniferin	Conifer bark, beet, asparagus and scorzonera	D-Glucose	Coniferyl alcohol	
Syringin	Lilac (*syringa*) jasmine and privet	D-Glucose	5-Methoxyconiferyl alcohol	
Picein	Willow and poplar	D-Glucose	*p*-Hydroxyacetophenone	
Gaultherin	*Gaultheria* species	Primeverose	Methylsalicylate	
Violutin	*Viola cornuta*	Vicianose	Methylsalicylate	
Spiræin (Helicin)	*Spiræa* species	D-Glucose	Salicyladehyde	
Scopolin	*Scopolia japonica*	D-Glucose	Aesculetin monomethyl ether	

was of exceptionally good quality, but was of a high price. Helicin, the glucoside of salicylaldehyde is one of the few optically active aldehydes which are easily obtained. (It is made by the oxidising action of dilute nitric acid on salicin). Its particular value lies in its ability to combine with racemic amines to give stereoisomeric aldimines which can be separated by fractional crystallisation.



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Cyanogenetic Glycosides

TABLE XI

Name	Source	Sugar	Aglycones
Amygdalin	Almonds and stone fruit kernels	Gentiobiose	HCN + benzaldehyde
Prunasin	Wild cherry-bark	D-Glucose	HCN + benzaldehyde (D-mandelonitrile)
Sambunigrin	Elder bark	D-Glucose	HCN + benzaldehyde (L-mandelonitrile)
Prulaurasin	Cherry laurel	D-Glucose	HCN + benzaldehyde (DL-mandelonitrile)
Vicianin	Vetch seeds	Vicianose	HCN + benzaldehyde
Phaseolunatin	Flax and seeds of *Phaseolus luteus* and *Heveâ braziliensis*	D-Glucose	HCN + acetone
Lotusin	*Lotus arabicus*	2 × *d*-Glucose	HCN + lotoflavin
Dhurrin	Sorghum and millet	D-Glucose	HCN + *p*-hydroxybenzaldehyde

Amygdalin was one of the earliest substances recognised as a glycoside. It had been known for some considerable time that the aqueous distillate of bitter almonds contained hydrocyanic acid, and further observations had been made on the isolation of benzaldehyde from the same source. It was Robiquet and Boutron-Chalard [1] who, after pressing the fatty oil from almonds, observed the marc to be without smell of either benzaldehyde or hydrocyanic acid until it had been moistened with water. They concluded that these substances were not present as such in the almond, but assumed that benzaldehyde was formed by the combination of water with a ' peculiar principle ' which they then endeavoured to isolate. Since water was obviously inadmissible for its extraction they used alcohol and extracted a crystalline nitrogenous substance to which they gave the name ' amygdalin '. They were astonished, however, to find that neither amygdalin nor yet the marc from which it had been extracted, gave benzaldehyde or hydrocyanic acid on treatment with water ; as they put it ' the prussic acid and oil of bitter almonds had vanished from our hands '.

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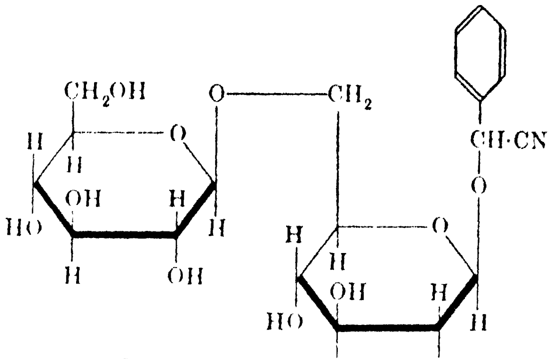
[1] Robiquet and Boutron-Chalard, *Ann. Chim. Phys.*, 1803, **44**, 352.

It remained for Liebig and Wöhler[1] to solve this problem. They observed that almonds contained a peculiar nitrogenous substance, 'emulsin', which in the presence of water converted amygdalin into benzaldehyde, hydrocyanic acid and glucose, a reaction which may be summarised :—

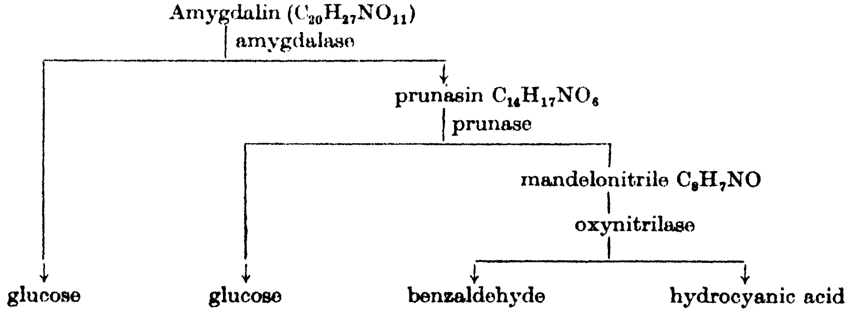
$$C_{20}H_{27}NO_{11} \longrightarrow C_7H_6O + HCN + 2C_6H_{12}O_6.$$

The presence of two molecular proportions of glucose in the products of hydrolysis of amygdalin (334) led to speculation for some considerable time until it was realised that they are present as the disaccharide gentiobiose. This has been



(334)

demonstrated by a variety of means ; methylation gives, on hydrolysis, a heptamethyl derivative yielding benzaldehyde, hydrocyanic acid, 2, 3, 4, 6-tetramethylglucose and 2, 3, 4-trimethyl glucose in equimolecular proportions. In addition, the sequential enzymic breakdown of amygdalin throws considerable light on its structure :—


Amygdalin ($C_{20}H_{27}NO_{11}$)
amygdalase
prunasin $C_{14}H_{17}NO_6$
prunase
mandelonitrile C_8H_7NO
oxynitrilase
glucose
glucose
benzaldehyde
hydrocyanic acid

The prunasin, prulaurasin and sambunigrin group are less complicated, being the D-, L- and DL- derivatives respectively of glucosidomandelonitrile. Vicianin is of interest as it represents the replacement of one glucose unit of amygdalin by arabinose ; in addition, it is unusual in that its enzyme vicianase, which occurs with it in vetch seeds, splits off the intact disaccharide.

Lotusin, a glycoside linking two of the families, is cyanogenetic and at the same time its aglycone is a tetrahydroxyflavone, a yellow pigment.

MUSTARD-OIL GLYCOSIDES

Many crucifers contain a glycoside which breaks down on hydrolysis to a thiocarbimide (or mustard oil) and glucose—together, in some cases, with other substances. These substances are responsible for the flavours of the various cresses and brassicas, including mustard, horseradish and others. Some of the more interesting of these glycosides are summarised in Table XII.

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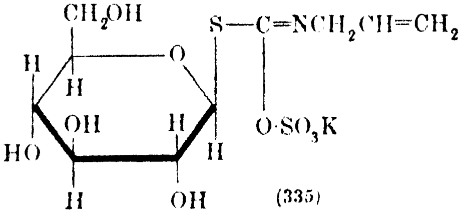
[1] Liebig and Wöhler, *Ann.*, 1837, **22**, 1.

TABLE XII

Name	Source	Sugar	Main aglycone	Subsidiary aglycone
Sinigrin	Black mustard (*Brassica nigra*) Horseradish (*Cochlearia armoracia*)	D-Glucose	Allyl thiocarbimide	$KHSO_4$
Sinalbin	White mustard (*Brassica alba*)	D-Glucose	*p*-Hydroxybenzyl thiocarbimide	+ acid sinapin sulphate
Glucotropæolin	Cress (*Lepidium sativum*)	D-Glucose	Benzylthiocarbimide	$KHSO_4$
Gluconasturtin	Nasturtium (*Tropæolum majus*)	D-Glucose		
	Watercress (*Nasturtium officinale*)	D-Glucose	Phenyl ethyl thiocarbimide	
Gluconapin	Rape (*Brassica napus*)	D-Glucose	Crotonyl thiocarbimide	
Glucocheirolin	Siberian wallflower (*Cheiranthus*)	D-Glucose	Cheirolin	
Erysolin	*Erysimum perowskianum*	D-Glucose	Homocheirolin	

Most of the aglycones of this group are particularly pungent, and in the case of sinigrin, the allyl thiocarbimide has been separated in considerable quantity for medical purposes. The structure of sinigrin is shown in (335) from which it will be observed that the glucose and potassium hydrogen sulphate group are virtually adducts at the =C=S group of the thiocarbimide. The presence of the sulphur link between the glucose and the remainder of the molecule has been confirmed by Schneider and Wrede,[1] who obtained thioglucose on reduction.



(335)

Sinalbin, from white mustard, is a more complex substance, and whilst it is fairly certain that the mustard oil and the glucose residue are united in the same way as those of sinigrin, the third moiety, sinapin acid sulphate, is a complex body which breaks down on treatment with baryta to sulphuric acid, choline and sinapinic acid, a dimethoxyhydroxycinnamic acid. Another point of interest are the cheirolin glycosides ; cheirolin and homocheirolin, depicted

$CH_3SO_2CH_2CH_2CH_2NCS$ (336)

$CH_3SO_2CH_2CH_2CH_2CH_2NCS$ (337)

in (336) and (337) are unusual in containing the sulphone group. They have both been synthesised,[2] and are probably representatives of a larger family of substances yet to be discovered. The occurrence of the sulphone group in plant substances is unusual.

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[1] Schneider and Wrede, *Ber.*, 1914, **47**, 2225.

[2] Schneider, *ibid.*, 1913, **46**, 2634.

Glycosides of the Plant Pigment Series

These are divisible into a number of families.

(1) The anthraquinone series.
(2) Chromone or benzpyrone glycosides, subdivisible into
  (*a*) the flavine series ;
  (*b*) the *iso*-flavine series ;
  (*c*) xanthone series.
(3) The anthocyanins.
(4) Indican.
(5) The polyene glycosides.

The Anthraquinone series comprise a group of substances which have tinctorial and purgative properties and have, therefore, been thoroughly examined. The best known of the series is probably ruberythric acid, which is found in madder-root. The extraction of a dyestuff, alizarin, from madder-root has been carried on since the earliest times, but it was Rochleder in 1851 [1] who first obtained the glycoside by extracting madder-root with boiling alcohol, obtaining an extract which, on cooling, gave ruberythric acid in glistening yellow needles. Hydrolysis gave alizarin and two molecules of hexose sugar which for many

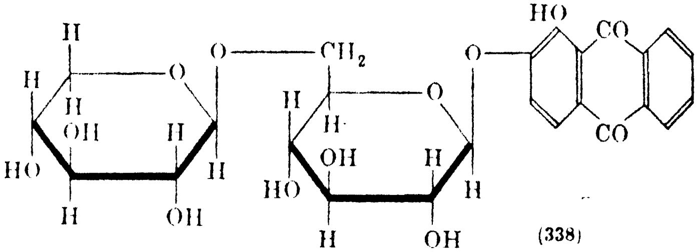

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TABLE XIII

Name	Aglycone	Derivative of anthraquinone	Sugar
Group I, from *Polygonaceæ*, *liliaceæ*, etc.			
Chrysophanin	Chrysophanic acid	4, 5-Dihydroxy-2-methyl	Glucose
Rhubarb glycosides	Rhein	4, 5-Dihydroxy-2-carboxylic acid	Glucose
Frangulin	Frangula-emodin	4, 5, 7-Trihydroxy-2-methyl	Rhamnose
Natalœin	Natalœ-emodin	3, 6-Dihydroxy-2-methyl	?
Barbaloin	Alœ-emodin	4, 5-Dihydroxy-2-hydroxy-methyl	D-Arabinose
Rheochrysin	Physicin	4, 5-Dihydroxy-7-methoxy-2-methyl	Glucose
Group II, from *Rubiaceæ*			
Ruberythric acid	Alizarin	1, 2-Dihydroxy-	Primeverose
From madder	Hystazarin	2, 3-Dihydroxy-	Glucose
Rubiadin	—	1, 3-Dihydroxy-2-methyl-	Glucose
Purpurin	—	1, 2, 4-Trihydroxy-	Glucose
Morindin	Morindone	1, 5, 6-Trihydroxy-2-methyl	2 × Glucose
Xanthopurpurin	—	1, 3-Dihydroxy-	Glucose
Munjistin	—	1, 3-Dihydroxy-2-carboxy-	Glucose

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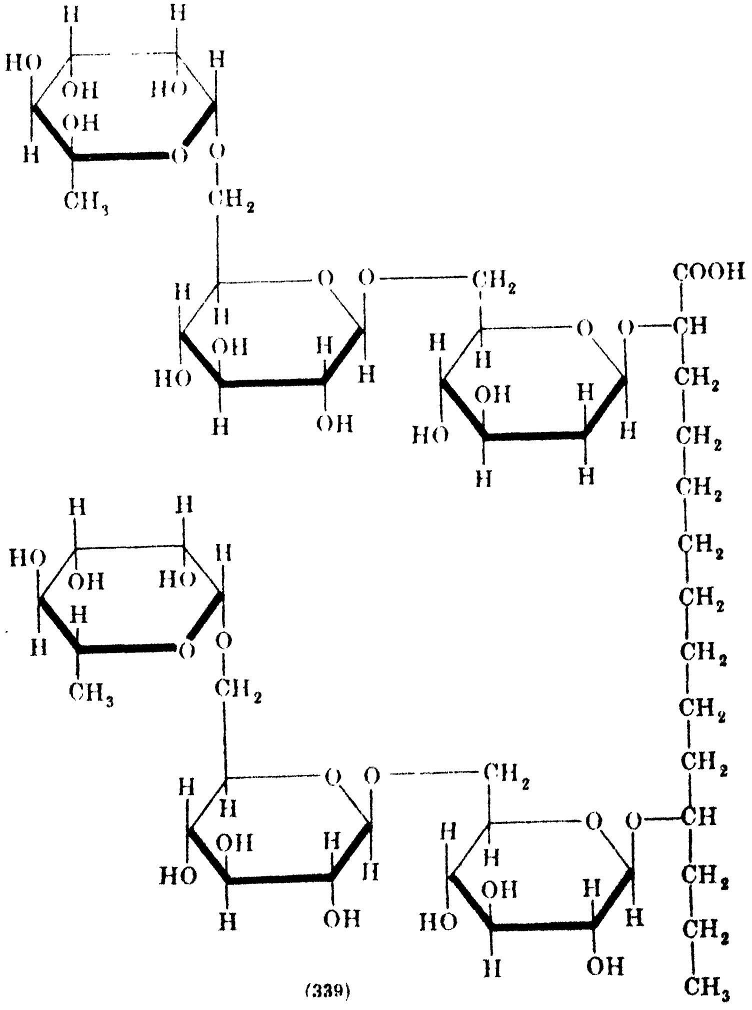
[1] Rochleder, *Ann.*, 1851, **80**, 321 ; 1852, **82**, 205.

years were thought to be two molecules of glucose. The work of Jones and Robertson[1] has shown that the sugars are D-xylose and D-glucose, and that the sugar in combination with the alizarin is primeverose ; the structure of ruberythric acid is therefore depicted in (338) both sugar links being of the 'β'- type.

Some of the better known glycosides of this series are set out in Table XIII. It will be seen that they fall into two groups, those from the *Rubiaceæ* being mainly 4, 5-hydroxy derivatives ; those from other orders being chiefly of the 1, 2- or 1, 3-type. The group has not been widely investigated, and difficulties have been met with in orientating the substituent groups in the substituted anthraquinone aglycones.

OTHER GLYCOSIDES

Mention has already been made in Appendix IV to Chapter V of the plant pigments derived from the oxygen rings. The vast majority of these exist as glycosides. The fact that these substances have been fully described previously makes further comment here unnecessary. The same is also true of the digitalis and triterpene saponin glycosides.



(339)

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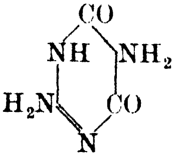
[1] **Jones and Robertson, *J.C.S.*, 1933, 1167.**

Of the other glycosides, examination of some of the natural purgatives have led to the discovery of interesting types. Thus, the jalap resin glycosides are powerful purgatives, and are related to the long-chain aliphatic acids. The majority of these glycosides spring from the order *Convolvulacœ* ; the jalap and scammony resins contain convolvulin, a complex glycoside from which the pure substance rhodoconvolvulic acid can be obtained ; on hydrolysis it yields one molecule of aglycone (2, 11-dihydroxypalmitic acid) and six sugar molecules —two rhamnose and four glucose. It is supposed that the sugar moieties are united through the two hydroxyl groups of the dihydroxypalmitic acid as trisaccharides as in (339). An ether-soluble glycoside is also obtained from crude convolvulin which contains the sugar epirhamnose, and similar glycosides from dihydroxypalmitic acid are known to occur in crude turpentine. The acid was synthesised by Votoček and Prelog.[1] Very similar in structure is the glycoside jalapin, which on hydrolysis yields D-glucose, rhamnose and D-fucose together with 11-hydroxyhexadecanoic acid ; [2] the pharbitinic acid of *Pharbitis* extract likewise gives D-glucose, L-rhamnose and 2, 11-dihydroxymyristic acid.

The nucleic acids contain a glycoside unit in their structures, but their study is deferred to Volume II. Several simple glycosides of this family are found in nature—for example, convicin, from the vetch, is a glucoside of alloxantin, and divicin of the diamine (340) ; even more remarkable is the substance hiptagin, a glucoside of the 3-nitropropionic acid (341). It will be noted that this substance is one of the few naturally occurring nitro-compounds.

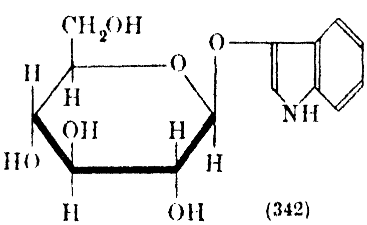


(340)

$NO_2CH_2CH_2CO$. O-glucose

(341)

Indican, the glucoside of indoxyl, was obtained by Schenk in 1855, but it was only at the turn of the century that its correct formula was deduced by Marchlewski and Radcliffe [3] as 3-β-glucosidoindoxyl (342). It is widely distributed in certain types of plants, from which it may be obtained in pale yellow crystals by extraction with hot alcohol. The chief plants associated with indican are the *Indigofera*—especially those species formerly cultivated for the production of indigo ; *Isatis tinctoria*, or the Woad plant, *Polygonum tinctorium*, and several of the *Orchidaceæ*.



(342)

There are innumerable glycosides of natural occurrence which have not been mentioned in the foregoing paragraphs ; many are, as yet, of indeterminate composition, whilst others have no particular point of interest to justify their inclusion, the vast majority are β-glycosides, and no fully authenticated α-glycosides are yet to be included in the heteroside family, although there is some *a priori* evidence that such a link may occur in seaweed glycosides, in steviosin, and in phillyrin, the characteristic glucoside of the *Forsythia*. From the point of view of carbohydrate chemistry, interest attaches to the common occurrence of rhamnose and of the hitherto very rare primeverose (6-glucosido-β-*d*-xylose) which proves to be quite widely distributed.

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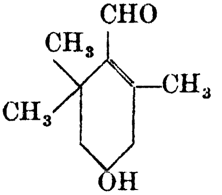
[1] Votoček and Prelog, *Coll. Trav. Chim. Tchécoslovakie*, 1929, **1**, 55.

[2] Davies and Adams, *J.A.C.S.*, 1928, **50**, 1749.

[3] Marchlewski and Radcliffe, *J.S.C.I.*, 1898, **17**, 434.

Another unusual glycoside is crocin, a pigment obtained from saffron, and the dried reproductive organs of many crocus species. It is a digentiobioside of crocetin (*q.v.*). It is of considerable biological interest (*a*) being one of the few polyene substances found naturally as glycosides, (*b*) in that its ingestion by animals enormously increases the motility of the sperm, dilutions of 1 in 10^6 *in vitro* still being effective in this respect. It is not inappropriate to recall the instinctive consumption of crocus by birds in the mating season, and the part played by saffron cakes and confections in the ancient fertility rites now merged in the festival of Easter.

Picrocrocine, a glucoside of 1-aldehydo-2, 6, 6-trimethyl-4-hydroxy *cyclo*-hexene (343) occurs with α-crocin in saffron, and is responsible for its unusual taste.



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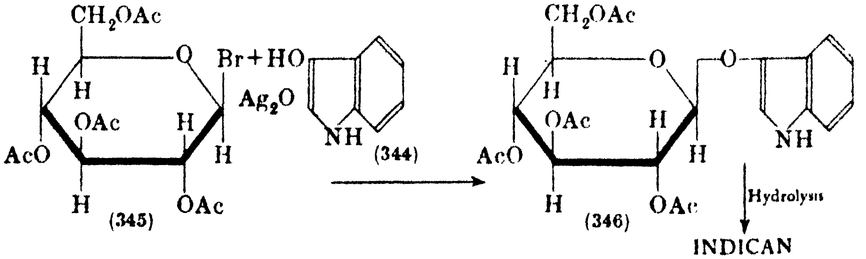
GLYCOSIDE SYNTHESIS

The synthesis of glycosides has been carried out mainly by two methods (*a*) enzyme action, and (*b*) the use of acetobromoglucose. This subject was developed by Bourquelot [1] and is largely concerned with the action of emulsin on a sugar and an aglycone ; in other words, advantage is taken of the fact that the reaction

$$\text{Glycoside} + \text{water} \underset{\text{emulsin}}{\rightleftharpoons} \text{aglycone} + \text{sugar}$$

is reversible.

The chemical synthesis of β-glycosides is effected by the condensation of acetobromoglucose with an aglycone in the presence of silver oxide. Thus indican may be obtained from indoxyl (344) and acetobromoglucose (345) by the interaction of their solutions in the presence of silver oxide. A tetra-acetyl indican is first formed (346) which is hydrolysed to indican, identical with that of natural occurrence.



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[1] Bourquelot (series 1912–1915).

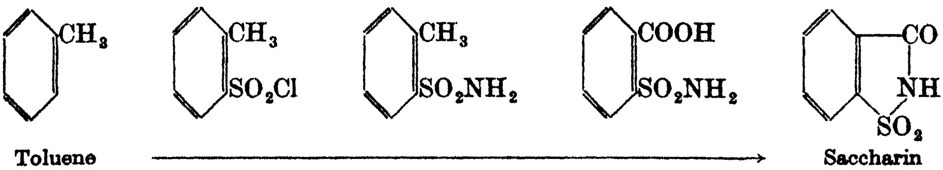
In this way a large variety of glycosides has been synthesised, including the cyanogenetic group prunasin, prulaurasin and sambunigrin,[1] and also amygdalin itself,[2] which was obtained by Campbell and Haworth by allowing acetobromogentiobiose to react with ethyl-DL-mandelate in the presence of silver oxide. An acetylated ethyl amygdalin is obtained which can be hydrolysed to amygdalin itself.

APPENDIX III

SWEETENING COMPOUNDS

The earliest compound of unusual sweetness to be discovered was saccharin. The scene of the discovery of saccharin was the Johns Hopkins University, Baltimore, and it was of especial interest to the University as the first discovery of major scientific importance made since the foundation of the laboratories three years previously, in 1876. Thus, in 1879, Remsen and Fahlberg discovered saccharin ; less fortunately, the discovery of its exceptional sweetness led to an undignified quarrel between the two scientists. It appears that after a hard day's work in the laboratory on some new sulphimides of the aromatic series Fahlberg went home and, after washing his hands carefully, sat down to supper. He noticed that the bread he was eating had a peculiar but unmistakable sweet taste ; since no-one else could taste this peculiar flavour, he was constrained to see whether it was due to traces of material carried from the laboratory on his hands which, indeed, he found to be the case ; and on placing the tip of the tongue on the hand or arm an intense sweet taste could be perceived. He thereupon returned to the laboratory and tested each of the various pieces of apparatus he had used during the day until he tracked down the sweetness to the substance which we now known as saccharin. The story of his difference of opinion with Remsen, who claimed to be a co-discoverer, is not worth retelling here.

As soon as saccharin became a commercial commodity—it was manufactured by Fahlberg and List soon after its discovery—all sorts of fantastic claims were made for it and, as usual, its reputation suffered considerably. It was soon found that, although minute traces of saccharin could sweeten a considerable amount of material, no nutritive contribution was made as in the case of sugar itself, and the possibility that saccharin itself could have a harmful action was mooted. Soon the new material came to be regarded as an adulterant, and its use was in some countries and states prohibited, in so far as foodstuffs generally were concerned ; import duties were imposed, and a stiff legal hedge began to grow up around its use. Surprisingly enough, the method of preparation introduced by its original discoverers is still used in its essentials, although the means by which the various transformations are achieved have altered. Thus, toluene is still the raw material, and is converted to its *ortho*-sulphonchloride ; thence to the sulphonamide and by oxidation to benzene-*o*-carboxy sulphonamide, a substance which readily loses water to form saccharin :—



Manufacture.—The original patented process of Fahlberg and List included directions for the sulphonation of toluene, using sulphuric acid at 100° C. and separating the organic sulphonic acids at the end of the process, by neutralising with lime, filtering the clear solution of the calcium salts of toluene sulphonic acid from the calcium sulphate sludge, and concentrating the filtrate to obtain the strong solution which could be converted into the sodium salts by double decomposition with sodium carbonate. The solubilities of the *ortho*- and *para*-toluene sulphonates of sodium had already been investigated in detail by Engelhardt and Latschinoff in 1865, so that it was easy for the original patentees to make use of the greater solubility of the *para*-compound in order to crystallise out a fairly pure *ortho*-compound. Fahlberg recommended oleum mixed with the ordinary acid, and claimed for the mixture a smoother sulphonation. A very detailed study of the sulphonation of toluene made by Holleman and Caland in 1911, proved that the yield of the *ortho*-acid diminishes as the temperature of sulphonation rises; consequently the use of elevated temperature or very strong oleum is precluded. Sulphonation is best accomplished at 0° C. with two equivalents of 100 per cent. acid. It is stated that the addition of kieselguhr, or bone charcoal or their equivalent, facilitates the progress of sulphonation by largely increasing the surface of toluene in contact with the acid.

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[1] Fischer and Bergmann, *Ber.*, 1917, **50**, 1047.

[2] Campbell and Haworth, *J.C.S.*, 1924, 1337.

Fahlberg subsequently protected the separation of the two isomers formed by means of the barium, aluminium, lead or magnesium salts, the latter base proving most successful. The sulphonation liquor is neutralised with sufficient lime to remove the free mineral acid, and the filtered liquor saturated with magnesium oxide or carbonate. On evaporation the *para*-compound crystallises, leaving the more soluble *ortho*-sulphonic acid in solution. The zinc salt has also been recommended for the same purpose. An alternative method is to use an excess of sulphuric acid (six parts of acid to one of toluene), and at the end of the sulphonation to run the mix into sufficient water to make the concentration of the residual acid 66 per cent. w/w; on cooling, the *para*-derivative alone crystallises. An improved process based on the same idea is to stir the mixed sodium salts thoroughly with four times their weight of 66 per cent. sulphuric acid; only the *para*-salt is decomposed, and goes into solution, leaving the *ortho*-compound insoluble and obtainable by centrifuging. Many other modifications of less importance have been devised.

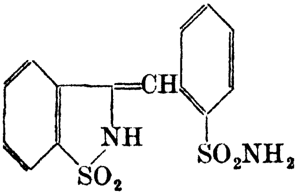
For conversion of the acid to its acid chloride Fahlberg used phosphorus trichloride and chlorine, or phosphorus pentachloride, distilling out the phosphorus oxychloride formed as a secondary substance during the reaction. Separation of the mixed chlorides could be effected by vacuum distillation and cooling, methods which were studied in detail by Ullmann and Lehner. Thann, Mulhouse et Cie obtained the chloride by the action of chlorosulphonic acid on the magnesium salt of the acid, and it is probably this fact which led to the discovery of Gilliard, Monnet and Cartier that toluene could be converted directly to the sulphonchloride by chlorosulphonic acid and allied materials without the intermediate isolation of the sulphonic acids themselves. Various reagents have been proposed for effecting this conversion, including pyrosulphuryl chloride in carbon disulphide solution, or carbonyl chloride, thionyl chloride or phosphorus oxychloride in the presence of sulphuric acid. The direct attack with chlorosulphonic acid is the easiest way of obtaining the toluene sulphonchloride, and is the method always used in practice.

Pure toluene is charged into the sulphonating pan, which can be both heated and cooled, and the chlorosulphonic acid is entered in a slow stream, being thoroughly mixed with the toluene and cooled with brine circulation to avoid any rise in temperature; hydrochloric acid gas escapes, and is passed up a small absorption tower; in this way the acid for the precipitation of the amide further on in the process can be obtained. It will be seen that since both *ortho*- and *para*-sulphonchlorides are produced by the process, some means of separation is necessary. Here again, much ingenuity has been expended in devising various methods for the separation of the two isomers, but the actual method used remains simple enough; the whole charge from the sulphonating pans is allowed to drop into a vat full of ice; the heat of hydration of the acid melts most of the ice; the *ortho*-sulphon-chloride remains liquid and the *para*-sulphonchloride (a solid, m. 69°) becomes solid. On passing the mix through a centrifuge the oily *ortho*-compound passes through with the water and the *para*-compound is retained. Actually the oil contains 80 per cent. of the *ortho*- and 20 per cent. of the *para*. In some works it is common to purify this oil by fractional distillation, but this is not really necessary, as the *para*-compound can be eliminated later in the process.

Fahlberg, in the original method, recommended ammonium carbonate for the amidation, and this is still used in most plants, since although dearer in price than ammonia in the anhydrous gas form, it is more convenient to use. Water is placed in the amidation kettle and sufficient ammonium carbonate added to give a solution of density 1·2; the *ortho*-sulphonchloride is added, and the whole mixture stirred with vigour; a little steam is occasionally required to start the reaction which sets in rapidly at 40°, the temperature soon rising to 80°. The temperature is allowed to drop a little and the clear liquid drained off from the separated solid amide through a suitable gauze-protected cock. Warm water and sufficient alkali are introduced to dissolve the amide, and after agitation to ensure complete solution the liquid is pumped off for oxidation. It must be remembered that the reaction mixture still contains some of the corresponding *para*-compound which will have to be removed at a subsequent point. Processes have been devised in which the *para*-compound is removed at the amide stage, this involving the separation of the two amides. In one process purification is effected by fractional precipitation of the alkaline solution with acid; the mixed amides (170 kg.) are dissolved, as already described, with the aid of water (300–500 litres), and sodium hydroxide (40 kg.) and the *ortho*-amide precipitated by the addition of hydrochloric acid (153 kg.; 20 per cent. HCl). The *para*-compound remains in solution, the method depending on the fact that the *para*-isomer has a much greater affinity for alkali than the *ortho*-compound. The *o*-amide melts at 155–156° and the *p*-amide at 137°; the melting point of a test sample is used as the criterion of the efficacy of the separation. Other methods of purifying the amide depend on the salting out of the *ortho*-amide from its solution in alkali by ammonium chloride; the *para*-compound remains dissolved under such circumstances. The whole of the amide of the *ortho*-isomer is not separated by this method, so that unless some method of recovery is practised, the process may be a wasteful one. Meister, Lucius and Brüning used a recovery process which involved the precipitation of the residual amides from the mother liquors with hydrochloric acid, and the reconversion of their ammonium salts to the sulphonchlorides with chlorosulphonic acid; the sulphonchlorides can then be reworked. All such processes are unnecessary if the separation is postponed to the oxidation stage. The amides form a eutectic with 60 per cent. of the *para*-isomer.

Three groups of methods are available for carrying out the oxidation: 1, with permanganate; 2, with chromate or chromic acid; 3, by electrolytic oxidation at the anode. Fahlberg and Remsen used potassium permanganate, and the same material is used in the majority of modern plants. In their original communication, Fahlberg and Remsen give no particular details of the preparation, but a later paper by Fahlberg and List, states that it is necessary to neutralise the alkali that is formed during the progress of oxidation; they also state that in acid solutions *o*-sulphobenzoic acid is formed. The method used in actual practice is to pump the caustic solution of the amides referred to above into a large kettle fitted with agitating gear and to stir vigorously while the finely powdered permanganate is added, maintaining the rate of addition of permanganate at such a rate that the temperature stays at 60°. The liquid is filtered from the manganese oxide in stoneware vacuum filters and the clear liquid is then blown into the precipitating vats. Sufficient hydrochloric acid is run in to precipitate the *para*-sulphobenzoic acid, which, unlike the corresponding amide, has a smaller affinity for alkalis. The saccharin is then precipitated from the residual solution. The saccharin so prepared is at least of 97 per cent. purity, and may be purified by recrystallisation up to 99·8 per cent.

It is only to be expected that patents have been taken out for the somewhat nebulous advantages attached to the use of other permanganates, ammonium, calcium and magnesium, whilst certain combinations of the electrolytic method and of permanganate oxidation have also been covered. Separation, too, of the *para*-compound by the use of alkaline earth salts has also been recommended. The oxidation is not so simple as it appears from the simple equation ; strict adherence to the directions both as to temperature and concentration must be insisted upon. One of the difficulties lies in the fact that if the solution is allowed to become acid during oxidation, or if other conditions particularly favourable supervene, a double compound of the formula



makes its appearance, and by its bitter flavour leads to an " after-taste " which is highly undesirable. Alternative methods of removal of the *para*-sulphamino benzoic acid include acetone extraction in which the *ortho*- is readily dissolved and the *para*-compound remains behind.

Bebie recommends the use of sodium dichromate in sulphuric acid as a suitable oxidising agent, and various other patented methods are based on a variant of such a process, ceric, ferric and chromic salts being recommended by the Usines de Rhône ; Altwegg and Collardeau and Orelup have devised similar methods, varying only in details. The great value of chromic oxidation is the great saving in cost when compared with permanganate ; it is doubtful if at the present moment chromic oxidation is used on an industrial scale. An extensive examination of the chromic method was made by Zaikov and Sokolov ; they pointed out that the chief difficulty lay in the fact that acids have a hydrolysing action on saccharin which results in the formation of the open chain compounds *o*-sulphobenzamide and *o*-sulphobenzoic acid, thus decreasing the yield ; they showed that if chromic oxidation is to be used commercially, then the temperature of oxidation must be kept below 60°, since at that temperature the rate of hydrolysis becomes appreciable. The best yields of saccharin were obtained by operating at 45° with sulphuric acid of 70 per cent. strength saturated with potassium dichromate at that temperature. Consistent yields of 90 per cent. are claimed. Zil'berg, using substantially the same process, achieved similar results ; it being observed that considerable loss of yield was encountered when sodium dichromate was substituted for the potassium salt. Later, Zil'berg and Magidson carried out an extensive investigation of the process of oxidation, using chromic acid in acetic acid solution, with traces of sulphuric acid present for the sake of its catalytic effect. Their general conclusion was that the temperature should be kept as low as possible to avoid the formation of by-products.

The work of Lowe attracted attention to the possibility of oxidising toluene-

o-sulphonamide to saccharin electrolytically. The oxidation was carried out in weak alkali carbonate solution, using small traces of lead, cerium or manganese salts as activators. Halla investigated the nature of anode materials in relation to the yields, and came to the conclusion that platinum was most suitable, gold being a good second ; erratic results were obtained with lead, and both tin and mercury were proved unsatisfactory. He could not obtain any confirmation of the activating effect of manganese or chromium ions ; similar conclusions were reached by Fitcher. Matsui, Sawamura and Adachi made a careful study of the electrolytic reduction of saccharin itself, and showed that a variety of products could be obtained. There is a most interesting Dutch patent covering the anodic oxidation of toluene-*o*-sulphonamide to saccharin in borate solutions, of which the *p*H is maintained at 9·5–14·1 ; the saccharin is removed from the cell by continuous electrosmosis ; it is not known that this process has been worked on a large scale.

In addition to the methods described above, there are innumerable so-called "alternative" methods for the production of saccharin ; many of these are simply academic exercises designed either to confirm the structure of the material or to illustrate some point of synthetic importance ; such methods are not described in detail here. Of the methods which have some possible industrial interest that of Lynde may be mentioned, since he advocates oxidation of the methyl group to carboxyl before conversion to the sulphonamide, although it is difficult to see any specific advantage in so doing.

Chemical and Physical Properties.—Saccharin forms large rhomboidal holohedral crystals, the crystallographic constants of which were determined by Pope ; subsequently crystallographic analyses have been made of the curious double compound of copper sulphate and saccharin, and of the triple complex between pyridine, copper and saccharin. There is a formal analogy between the crystal structure of saccharin and phthalimide, which was investigated by Jaeger. The crystals of saccharin show the phenomena of triboluminescence (generation of light on fracture). The melting point of saccharin has been given variously at figures ranging from 220-229°, but the usually accepted figure is 228·5°. The lack of sharpness is in all probability due to divergences in the rate of heating, since at the melting point a slight decomposition takes place which may form products which, on slow heating, depress the melting point. Saccharin may be sublimed in a vacuum ; liquid crystals are formed when saccharin is melted with cholesterol.

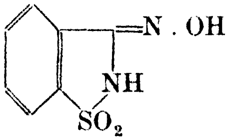
Saccharin is but slightly soluble in water, and a recent determination by Bebie shows that at 10° one part of saccharin dissolves in 325 parts of water ; at 100°, the solubility is one part in 30 parts of water.

It has been suggested that when foodstuffs preparations are compounded with small quantities of saccharin, there is some considerable risk of the saccharin being destroyed during the cooking or processing. Thus, a direct statement was made by Carlinfanta and Scelba to this effect, but was refuted by Condelli. The subject was closely investigated by Täufel and various collaborators, who came to the conclusion that the danger of such decomposition was negligible. Thus, he heated solutions of strengths from N/100 to N/1000 for 2 hours at various temperatures and found the following decompositions :—

Temperature °C.	Amount (%) Decomposed
100	Nil
125	12
150	56
200	75
250	88

The amount of decomposition was measured spectrophotometrically as well as by chemical means, so that by cooking at 100° there is little danger of decomposing aqueous solutions of saccharin ; on the other hand, food preparations contain a number of highly reactive chemical substances which at the temperature concerned may not decompose the saccharin, but may react with it ; this point should be experimentally investigated in the case of formulæ involving the use of saccharin in the presence of other chemical substances at temperatures above 90° C. It was shown by Preiss and Täufel that the decomposition of saccharin proceeds more rapidly in slightly alkaline solutions.

Chemically, saccharin does not present many problems of interest ; it is tautomeric, a property which has been investigated by Heller and others ; it forms salts, the ammonium salt being a trade preparation under the name of "Sucramin", and the sodium salt is widely used, being much more soluble than the base itself. It is usually referred to as "soluble saccharin", or "crystallose" ; actually, the base can form salts with several molecules of an alkali metal, but the monosodium salt is used exclusively in commerce. It is not proposed to deal with the many experimental investigations which have been made on the derivatives of saccharin, although it may be permissible to draw attention to the unusual activity of the carbonyl (=CO) group in the ring. This is unusually active, and will react with amines such as aniline ; it has sufficient ketonic properties to form an oxime which has been the subject of a very detailed series of investigations by Mannessier-Manelli.



Saccharin oxime

Physiological Properties.—Consideration of the physiological properties of saccharin may be divided into three sections, (*a*) the effect of large doses of saccharin on the animal system, (*b*) the effect of small doses similar to the quantities likely to be consumed when saccharin is used as a sweetening agent, and (*c*) the sweetening action of saccharin.

In the first instance, some early work of Roger and Garnier showed that saccharin can act, although to a somewhat less extent, in the same way as hydrochloric acid, as a co-enzyme to pepsin in the digestive juices ; this is, however, only to be expected from the fact that saccharin is an acid, and gives hydrogen ion in solution. Stein made the statement that saccharin actually inhibited the action of the digestive juices and started a controversy that lasted for many years. The implication that saccharin interfered in any way with the activity of the digestive tract was vigorously denied by the manufacturers of the material and those who examined the material from a physiological standpoint, and one investigator showed that, in addition, saccharin was less toxic to vegetable organisms than sodium benzoate. Thus, while Meillière condemns its use (on hypothetical grounds), Best declared it to be harmless, and Blodgett, who in 1920 carried out a series of feeding tests with saccharin, came to the same conclusion. The question was reopened in the same year by Becht, who experimented on the effect of saccharin on the catalase of the blood, and showed that on intravenous injection of the saccharin a slight decrease of blood catalase effect was to be observed. His experiments, few in number, and only very small in the extent of the recorded change, proved, in reality, very little, since the concentration of saccharin in the blood under the conditions of the experiments was so great as to be impossible of attainment from the normal consumption of traces of saccharin in foods. Be that as it may, however, his work served to stir up the old problem, and various investigators applied themselves anew to the solution of the question as to whether saccharin is toxic.

Some pointed out that much of the inconsistency of previous experimental work was due to failure to take into account the acidity of saccharin ; Miyadera gave dogs 0·4 gm. per kilo. on 7 successive days, and failed to note any change in the nitrogen balance ; Eweyk showed that there was no cardiac effect even in large doses ; Haramaki showed that the only effect was a slight increase in the gastric secretion when applied in large doses ; Schwarz and Steinmetzer confirmed this, and showed that saccharin had no effect on diastatic, tryptic or peptic digestion ; much other confirmation followed. There was still, however, a "minority report" against the use of saccharin ; Carlson could not recommend its continued use ; and Heitler put forward the extraordinary (and hitherto unconfirmed) theory that saccharin is a heart depressant, even in small doses.

An unfortunate poisoning case with saccharin served to focus more attention on the matter. A boy of nine ate, in the course of an afternoon, 200 saccharin tablets containing, in all, 3·5 gm. of saccharin itself and 10·5 gm. of sodium bicarbonate. Delirium and hallucinations were observed, together with a large urticaria which contained coagulated serum. The condition rapidly responded to local treatment and a rapid recovery followed. Whilst the dose is large (in particular when considering the age of the child), this finally disposes of the argument that saccharin cannot under any circumstances cause physiological symptoms.

The question still remained open, however, as to the probability of the small quantities of saccharin taken as a sweetening agent causing any physiological disturbance ; and this appears to have been disposed of by the long series of experiments carried out by Nito and by Fantus and Hektoen. The former investigator experimented on dogs. The animals were given five tablets daily at the commencement of the experiment, and ten tablets later on, so that in 100 days each dog had received 600 tablets, each containing 0·035 gm. of saccharin, or 21 gm. The only abnormal condition when in post-mortem examination was a diffuse hyperemia in the kidneys ; this, although slight in extent, was more apparent in the glomeruli than elsewhere, and was ascribed by this investigator to difficulties of excretion, since it has been shown that saccharin is not easily broken down in the animal organism, but is to a large extent excreted unchanged. In view, however, of the large doses used, the work of Fantus and Hektoen is of interest. Their test subjects were rats, of which three large groups were taken. One group fed on a normal diet with no saccharin were kept as a control ; the second group received the same diet to which was added 1 per cent. by weight of saccharin, whilst a third group received 10 per cent. by weight. No difference could be detected in any way between the first and second groups, after 252 days medication in which the second group had consumed an average of 31 grams of saccharin. In the third group a slight reluctance to feed was noticed, but after the same period and the consumption of over 300 gm. of saccharin no post-mortem lesions could be detected. Lehmann carried out the same type of experiment with mice, carrying the observations over three generations, no abnormalities at all being shown. Other data has also been obtained on the same lines. From a veterinary standpoint, Jagoda reports definite advantages in growth by the addition of 2 gm. daily of saccharin to the feed of beast.

The whole evidence, when critically sifted, goes to show that in the quantities likely to be consumed, assuming an otherwise normal diet, pure saccharin is harmless.

Saccharin is not the only substance of high sweetening power ; there is a natural glycoside—obtained from the leaves of *Stevia rebaudiana* [1]—which is

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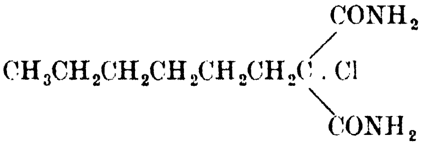
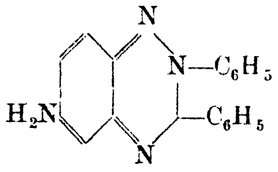
[1] Anonymous, *Bull. Imp. Inst.*, 1920, **18**, 123.

150-200 times as sweet as sugar. This substance, which is contained in the leaves to an extent of 20 per cent. of their dry weight is called 'stevioside', has a formula $C_{38}H_{60}O_{18}$, and is rapidly hydrolysed to three molecules of D-glucose and one of steviol, $C_{20}H_{30}O_3$, $[\alpha]_D - 94{\cdot}6°$; practically nothing is known of the structure of steviol.[1] Again the anti-aldoxime of perilla aldehyde (see p. 702) is 2000 times as sweet as sucrose; no synthesis of this aldehyde has been reported, and its preparation from natural sources is difficult. The small quantity of the oxime which has reached commercial channels is called 'peryllartine'.



$$CH_3CH_2CH_2CH_2CH_2CH_2C(Cl)(CONH_2)_2$$

(347)



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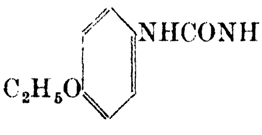

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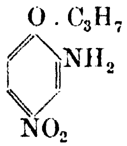


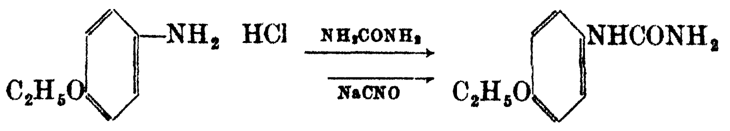
(349*a*)

Of the purely synthetic substances, three are of interest, namely, *n*-hexylchloromalonamide (347), which is about 300 times as sweet as sucrose; aminodiphenyldihydrophenotriazine (348) which, as 'glucin', made a brief excursion into industrial circulation, and which is about 100 times as sweet as sucrose; and dulcin, *p*-phenetylurea, which is about 225 times as sweet as sucrose.

Of these substances, only dulcin (349) is of industrial importance; although only half as sweet as saccharin, its 'sweetness' much more closely resembles that of sugar than does the somewhat aromatic flavour of saccharin, which latter has a quite appreciable bitter 'after-taste'. The discovery of dulcin and of its sweet taste was made in 1883, 4 years after the discovery of saccharin, by Berlinerblau.[2] It was introduced into Continental manufacturing practice by Riedel, A.-G., as 'dulcin', and by von Heyden as 'sucrol'. Introduction into British manufacturing practice was made by Genatosan Ltd.

Mention must also be made of the recent discovery by Verkade of the sweet taste of *n*-alkoxy-2-amino-4-nitrobenzenes, the *n*-propyl compound (349*a*) being 4000-5000 times as sweet as sugar; it has, at the same time, powerful local anæsthetic properties.

The manufacture of dulcin is carried out either by heating *p*-phenetidine with urea, or by condensing a solution of its hydrochloride with sodium cyanate. The latter is slightly more expensive to operate, but yields a better quality product:—



Considerable ingenuity has been applied to the investigation of substances related in structure to the various classes of sweet compounds, in order to ascertain what relation there may be between the sweet taste and the chemical structure. In spite of the extensive researches of Cohn and Holleman the answer is that no obvious relation can be detected.

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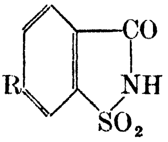
[1] Bridel and Lavieille, *C.R.*, 1931, **192**, 1123.
[2] Berlinerblau, *J. Pr. Chem.*, 1884, 2, **30**, 97.

de Roode[1] successively replaced the group R (350), i.e., the ' 4 ' position by fluorine, chlorine, bromine and iodine, and found that whilst 4-fluoro saccharin resembled saccharin very much, the other halogen compounds became progressively less sweet.

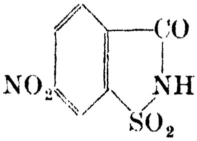


(350)

It remained for Holleman to determine the influence of *position* of entering groups on sweetness. Although he was unable to obtain 3-chlorosaccharin, he prepared the other isomers, and observed the following properties :—

4-Chlorosaccharin	Fairly sweet.
5-Chlorosaccharin	Only feebly sweet.
6-Chlorosaccharin	More than half as sweet as saccharin, but with an astringent after-taste.

In addition, he found that introduction of various other groups into the benzenoid ring of saccharin, resulted in large modifications of the taste of the products. Nitrosaccharin (351) is intensely bitter, but its reduction to aminosaccharin (352) furnishes a compound which is even sweeter than saccharin. The introduction of alkyl groups seems to have little or no effect on the sweetness of the product ; so that methyl- and ethylsaccharin (353) are comparable in sweetness with the parent body. The alkyl groups modify the after-taste of the compound, rendering it, in the case of methylsaccharin, slightly less aromatic. On the other hand, the naphthalene analogue of saccharin (354) has a bitter taste.



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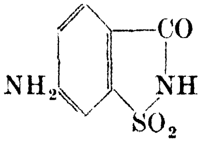

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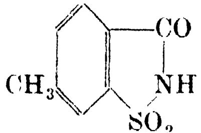

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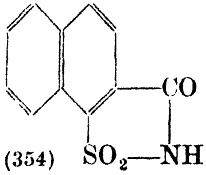
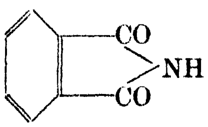


(354)

A second line of research, pursued by Holleman, is multiplication of " sweetening " groups in the compound. It may be argued, since phthalimide (355) is tasteless, and saccharin (356) sweet, that the sweetness of the latter is due in some way to the presence of the SO_2 group—but on introducing two SO_2 groups, a substance is obtained—benzene-*o*-disulphimide (357), which is only half as sweet as saccharin. Its sweet taste could just be perceived at a dilution of 1 : 1000, so that its sweetness was of the same order as that of dulcin. Further experiments elicited the fact that multiplication of the saccharin groups is scarcely ever associated with increase of sweet taste. For



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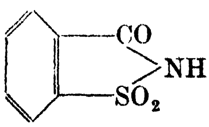

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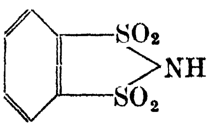

(357)

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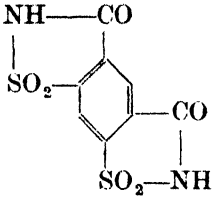
[1] de Roode, *Am. Chem. J.*, 1891, **13**, 218.

example, of the compounds indicated below (358) had a definitely bitter taste, while (359) had a sweetish astringent taste, in no way comparable with that of saccharin.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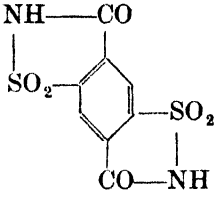
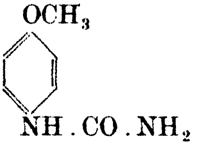

(359)

With sweet compounds of this type it has been noticed that the replacement of an oxygen by a sulphur atom, or of a sulphur by a selenium or tellurium atom, modifies the taste of the compound; *para*-anisyl urea (360) and *para*-phenetyl urea (361) are sweet, but the corresponding thioureas (362) and (363) are bitter ; moreover, selenosaccharin tastes bitter (364).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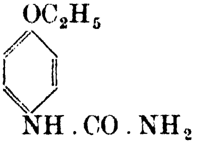
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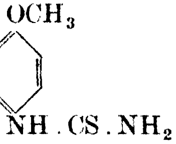
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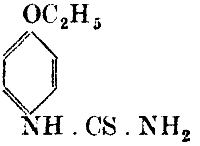
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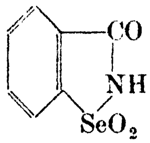
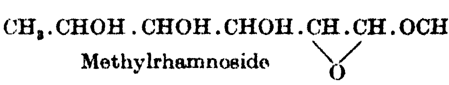

(364)

No account of this subject is complete without some reference to the work of Sternberg on the sweet taste of aliphatic compounds. Sternberg points out the interesting generalisation that for an aliphatic compound to be sweet, the carbon atoms must not outnumber the hydroxyl groups by more than one, or the combination will be bitter. He adduces numerous examples in support of this, among them the fact that while rhamnose is sweet, methylrhamnoside is bitter :—

$CH_3.CHOH.CHOH.CHOH.CHOH.CHO$

Rhamnose


$CH_3.CHOH.CHOH.CHOH.CH.CH.OCH_3$ (with the two CH groups bridged by O)

Methylrhamnoside

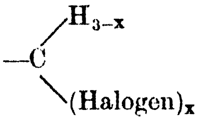
Again, he has pointed out that the sweetness of a compound increases with the number of hydroxyl groups present. Thus, glycol is sweet, but not so sweet as glycerol, which, in turn, is less sweet than glucose.

The conclusion obtrudes itself that a small difference in structure has a large influence on the sweetness of a compound, a fact observed among other phenomena relating to physiological action. Thus, saccharin is 500 times sweeter than sugar, the corresponding *para*- compound is tasteless. The conclusion follows, therefore, that the perception of sweet taste is related more to the intramolecular movements than to the more obvious structural details of the molecule.

Oertley and Myers postulate that sweet taste depends on two chemically distinct groups, the presence of which in conjunction is necessary for the development of sweet taste. They term these two groups " glucophore " and " auxogluc " . . . a terminology borrowed from the colour-constitution analogy.

They define a "glucophore" as a group of atoms, which has the power to form sweet compounds with a number of otherwise "tasteless" groups of atoms—these latter being the "auxoglucs". The following groups are found to be glucophores, in their sense :—

(1) —CO—CHOH (*H)
(2) —COOH——CHNH$_2$
(3)



$$—C\begin{matrix}\diagup H_{3-x}\\ \diagdown (Halogen)_x\end{matrix}$$

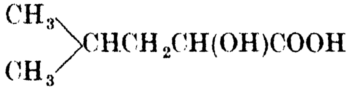
(4) CH$_2$OH—CHOH—
(5) CH$_2$—O . NO$_2$

The (*H) in the glucophore (1) is meant to signify that the groups must be attached to one hydrogen at least, before its glucophoric function can be realised. The following groups are deemed to be auxoglucs :—

(1) Hydrogen.
(2) Alkyl carbon chains, such as $CH_2CH_2CH_2$.
(3) Monohydric alcohol residues, e.g., $CH_2OHCH_2CH_2$.
(4) Polyhydric alcohol residues, e.g., $CH_2OHCHOH$.

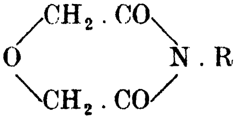
They adduce much evidence to show that combination of a glucophore with an auxogluc produces sweetness ; but their theory has many disadvantages, among them the fact that it takes no account of the many aromatic substances, among them saccharin, whose sweetness cannot be so easily explained. In the second place the definitions of auxogluc and glucophore are so loose and vague, that it is difficult to find a compound that cannot be made up from them, in fact, nearly all the aliphatic compounds would be predicted, on this theory, to be sweet, although in reality but a few of them are.

Many interesting cases of sweet taste in the aliphatic series have been recorded, although no practical application has been made of them. Thus Skrabal and Flach[1] investigated the *dextro*-α-hydroxy*iso*hexoic acid (365) compounds and found the sodium salt to be ten times as sweet as sucrose ; the L- form is much less sweet. Sido[2] has prepared a series of esters of diketo paroxazine (diketomorpholine) (366) which are considerably sweeter than sugar ; the propyl derivative is the sweetest, more or fewer carbon atoms in the alkyl group decreasing the sweet taste.



$$\begin{matrix}CH_3\diagdown\\ CH_3\diagup\end{matrix}CHCH_2CH(OH)COOH$$

(365)



(366)

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[1] Skrabal and Flach, *Monatsh.*, 1919, **40**, 431.
[2] Sido, *Ber. deut. Pharm. Ges.*, 1921, **31**, 118.

CHAPTER XI

STEROIDS AND OTHER SUBSTANCES OF BIOCHEMICAL INTEREST

In this chapter are grouped together a variety of substances which, although not of necessity related chemically, have a special interest for their biochemical significance. Since the discovery of adrenalin, it has been shown that chemical substances may be synthesised by living matter for specific purposes, and the name "hormone" was given to adrenalin as the first of these "chemical messengers". Other hormones were soon discovered, and although the chemical structure of many yet remains undiscovered, sufficient have been synthesised to show that they are not necessarily of direct chemical interrelation. At the same time, it was ascertained that traces of certain complex organic substances are essential to the growth and health of organisms, and that whilst in most cases sufficient of these substances are taken in with the food, in abnormal conditions their absence may give rise to what are known as "deficiency diseases", the existence of which is specifically due to the absence of the essential chemical factors, termed vitamins. There seems little functional difference between hormones and vitamins, and the groups may be regarded as belonging to a large class of bodies, traces of which must be present for the normal existence of the organism. The fundamental difference between the two groups is that the hormones are produced within the organism, and that the vitamins are not so produced, but are taken in with food. It has been proposed to divide this large class of compounds into three sections :—

1. *Endogenous Hormones.*—Previously known simply as "hormones", and constituting those vital factors which are commonly produced by animals through their ductless glands.
2. *Exogenous Hormones.*—Including the vitamins or food accessory factors ; produced to a large extent externally.
3. *Phytohormones.*—Substances which control and stimulate the growth of vegetable cells.

It is proposed to arrange the matter of this chapter in the above manner, and to consider in addition the large family of steroids and related compounds, which for convenience are again subdivided thus :—

1. True sterols.
2. Bile acids.
3. The vitamins D.
4. The sex hormones.
5. Saponins.
6. Cardiac poisons.
7. Toad poisons.
8. The carcinogenic hydrocarbons.

It will be seen, since certain vitamins and hormones are steroid in nature, that the groups overlap a little ; to avoid duplication, steroid hormones and vitamins are dealt with in the steroid section.

THE VITAMINS

So far back as 1881 Lunin, working under v. Bunge in Basle, observed the necessity for some nutritional factors other than the conventionally accepted proteins, fats, carbohydrates and inorganic salts, in the maintenance of life. He used pure substances in building up a rat diet and, although he had made adequate provision of the four major factors mentioned above, his animals went into a rapid decline which could be dramatically arrested by the inclusion in the diet of a small amount of fresh milk. His interpretation of the results was that certain essential nutrients existed, which were present in minute quantity, and whose nature and essentiality had hitherto been unsuspected.

All this was set out in v. Bunge's textbook of physiological chemistry, and the work was repeated by Pekelharing in 1905, whose interpretation was similar. It remained, however, for Gowland Hopkins to designate these essentials, "accessory food factors", and to develop and popularise the earlier work. Subsequently the name "vitamines" was proposed by Funk under the impression, afterwards found untrue of many of them, that they were nitrogenous substances. The shorter name has, however, come into general use and has been altered to "vitamin" in order to avoid confusion with the amines. It was soon recognised that these substances could be divided into two main groups :—

(*a*) Those soluble in water (water-soluble vitamins).

(*b*) Those soluble in oils and some other organic solvents, but sparingly or practically insoluble in water (fat-soluble vitamins).

The former group was early recognised as containing two chief members, called water-soluble B and water-soluble C, the former occurring in the pericarp of cereals such as rice, etc., in yeast and in many other nitrogenous food-stuffs, and the latter (water-soluble C) occurring in many green vegetables and in many fruits such as lime, lemon and orange. Subsequent work showed that the so-called vitamin B was in reality a mixture of at least nine vitamins having different functions in the maintenance of health and of widely different chemical nature. Of these, the structure is known and has been confirmed by synthesis in the case of B_1, B_2, biotin, pyridoxine, nicotinic acid, pantothenic acid, inositol and *p*-aminobenzoic acid, and it is interesting to notice that the water-solubility of these vitamins is due to quite different causes. B_1 owes its solubility in water to the fact that it is the dihydrochloride of a diamine, and is therefore of the nature of an ammonium salt, whereas B_2, though a nitrogenous compound, apparently owes its solubility to the presence in the molecule of an aliphatic chain containing four hydroxyl groups ; the others owe their solubility to carboxyl, or hydroxyl groups.

The solubility of vitamin C in water is also due to an aliphatic polyhydroxy chain, this substance being closely related to the hexose group of sugars and having a much simpler chemical constitution than many other vitamins of known structure.

With regard to the oil-soluble vitamins A and D, these were not first recognised as different entities, but since the recognition of their separate chemical and physiological nature, it has now been demonstrated that vitamin D activity appears to be confined not to a single individual, but to a number of very closely chemically related compounds having similar or identical physiological activity. Both vitamins A and D are of the nature of very complex hydrocarbon groups containing a single alcoholic hydroxyl group, and from this their insolubility in water and solubility in fats will be readily understood.

From the foregoing it will be seen that great structural diversity exists between vitamins of various classes, and only the adventitious circumstances of their mode of occurrence in nature in minute quantities in various foodstuffs and their function as necessary accessory factors for the maintenance of health brings them together under the same heading. No further excuse, therefore, need be offered for dealing with them in the following sections, alphabetically. Vitamin A has already been discussed (p. 733) in connexion with those terpenoid compounds with which it is intimately related.

VITAMIN B_1 (ANEURIN)[1]

When, in 1897, Eijkmann in Java first correlated polyneuritis in fowls with a dietary deficiency, little attention was then paid to his results ; these results were, nevertheless, tantamount to the first observation of the existence of a deficiency disease (beriberi) caused by the absence of a vitamin. The pure crystalline substance was isolated from rice husks by Jansen and Donath [1] in 1926. and by Windaus and his co-workers [2] from yeast several years later. However, the work carried out by Williams and his many colleagues between 1932 and 1937 on the chemical nature of vitamin B_1 has finally led to the elucidation of its structure and to its synthesis.

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[1] Nomenclature of aneurin, see Jansen, *Nature*, 1935, **136**, 259.

It has been established between 1910 and 1912 that infant mortality in Manila (which was at that time 50–55 per cent.) was almost entirely due to the disease beriberi. The condition could be relieved and ultimately cured by addition to the diet of a small quantity of extract of rice polishings (the powdered pericarp of the grain, removed during polishing). Hence it is not surprising that the first problem confronting the investigators was the extraction of the anti-beriberi factor (vitamin B_1) from the crude extract of rice polishings, where it occurs to the extent of 1 part of vitamin in 50,000. The preparation of comparatively large quantities of vitamin B_1 by Williams and others in 1933 led to the establishment of its empirical formula as $C_{12}H_{18}ON_4Cl_2S$.

The first light shed on the structure was an interesting cleavage with sodium sulphite solution at $p\text{H} = 5$ when two simpler substances are produced quantitatively : —[3]

$$C_{12}H_{18}ON_4Cl_2S + Na_2SO_3 = \underset{(a)}{C_6H_9N_3SO_3} + \underset{(b)}{C_6H_9NSO} + 2NaCl$$

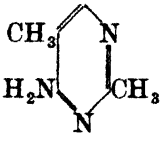
Product (*a*) has the following reactions :—

(1) Heated under pressure with water, sulphuric acid is produced.
(2) Fused with alkali, a sulphite is obtained.
(3) With aqueous hydrochloric acid, ammonia is formed thus :—

$$C_6H_9N_3SO_3 + HCl + H_2O = \underset{(c)}{C_6H_8N_2SO_4} + NH_4Cl$$

Product (*c*) also gave reactions (1) and (2) above, from which it is clear that both (*a*) and (*c*) contain the sulphonic acid group.

(4) The ultra-violet absorption spectrum of (*a*) points to a pyrimidine structure, and reduction with sodium in liquid ammonia yields a base 2, 5-dimethyl-4-aminopyrimidine (1), identical with the synthetic material.



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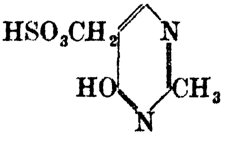

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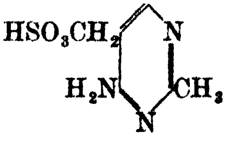

(3)

Further, 2-methyl-6-oxy-5-pyrimidine methyl sulphonic acid (2) was synthesised and shown to be identical with the compound (*c*) referred to above, thus establishing the formula of (*a*) as the corresponding 6-amino derivative (3).

The portion (*b*) proved to be a thiazole and a primary alcohol, and on oxidation gave 4-methyl thiazole-5-carboxylic acid (4) prepared many years ago by Wohman, pointing to the structure (5) for the product itself.

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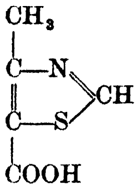
[1] Jansen and Donath, *Verslagen. Konin. Akad. Wetenschappen* (Amsterdam), 1926, **35**, 923.

[2] Windaus *et al.*, *Z. physiol. Chem.*, 1932, **204**, 123.

[3] Williams, *J.A.C.S.*, 1935, **57**, 229.



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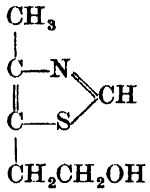
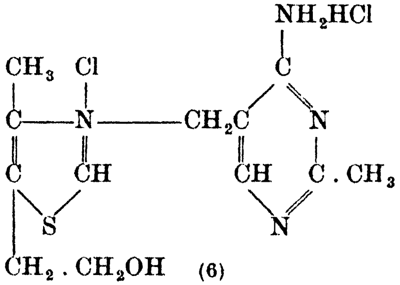


(5)

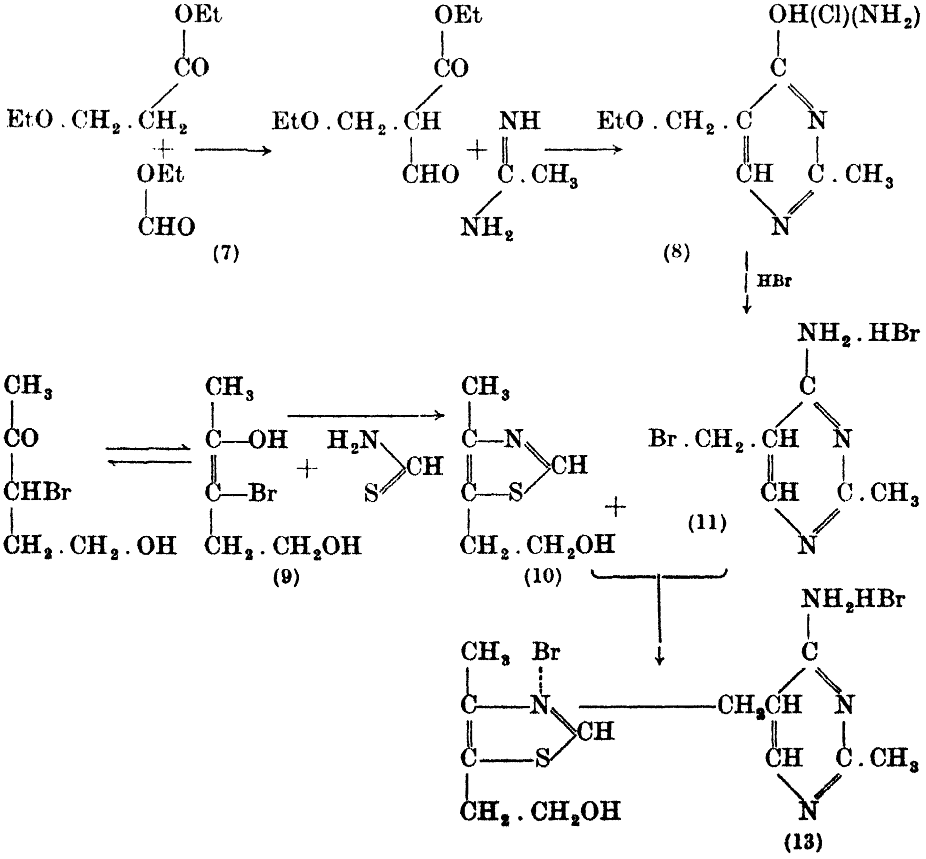
This was confirmed by synthesis and the structure (6) :—



(6)

has been adopted for vitamin B_1 itself. This also has been confirmed by synthesis :—

Ethyl formate and ethyl-β-ethoxypropionate are condensed in the presence of sodium ethoxide to give ethyl-formyl-β-ethoxypropionate (7) :—



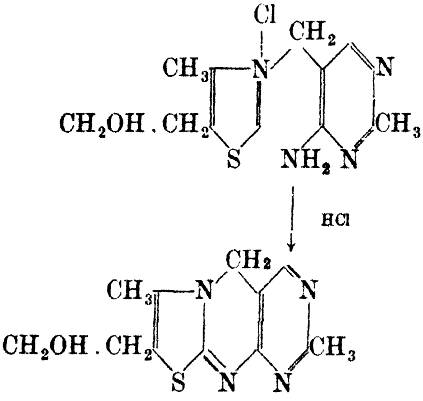
(7) (8) (9) (10) (11) (13)

Vitamin B_1 Bromide hydrobromide

This reacts readily with acetamidine to give 2-methyl-5-ethoxy-methyl-6-oxypyrimidine (8). The —OH group of this compound may be converted successively to "—Cl" and "—NH_2" by treatment with phosphorus oxychloride followed by ammonia, after which concentrated hydrobromic acid will remove the ethoxy group, replacing it by bromine. In this way, 2-methyl-5-bromomethyl-6-aminopyrimidine hydrobromide, (11) is obtained and is warmed with 4-methyl-5(β-hydroxy)ethyl thiazole (10) itself obtained from thioformamide and bromo-acetopropylalcohol (9). The union of (10) and (11) yields the vitamin bromide hydrobromide (13) converted by agitation with a suspension of silver chloride to the vitamin chloride hydrochloride, isolated as colourless needles.

The physiological action of vitamin B_1 is not fully understood, nor is it within the scope of this book to review the work already done. Nearly all living material, both vegetable and animal, uses vitamin B_1 for its life processes, and it has been shown that in its absence, pyruvic acid accumulates in the tissues and blood. Löhmann and Schuster go so far as to consider the pyrophosphoric ester (15) of vitamin B_1 as the prosthetic group of the enzyme responsible for decarboxylating pyruvic acid (cocarboxylase). Be that as it may, the synthetic product has found rapid application for the therapeutic control of beriberi in Japan and the Phillipines, the current incidence of which in the latter is placed at 150,000 cases.

The structure of thiochrome, a yellow pigment very closely associated with vitamin B_2[1] has been shown to be (14) and its formation is indicated thus :—



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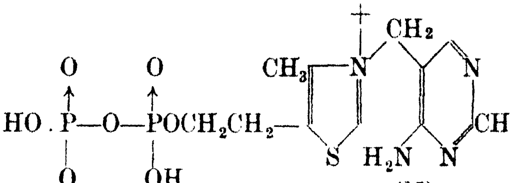

(15)

The oxidation of vitamin B_1 to thiochrome can be carried out readily by alkaline ferricyanide.[2]

Vitamin B_2 and the Flavins

Many animal and vegetable substances owe their pale yellow colour to the presence of a group of pigments of the flavin type. These have been isolated from yeast, milk, egg-yolk, liver, malt and urine, and the main groups of such pigments are as follows :—

1. Free flavins (lactoflavin D from milk and ovoflavin).
2. Flavins combined with purines (lactoflavins A, B and C).
3. Flavins combined with proteins (from milk, Warburg's pigment, yeast and animal cells).
4. Lumiflavin.

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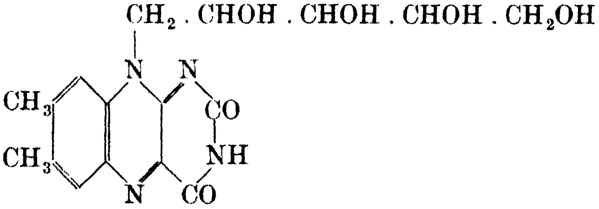
[1] Kuhn *et al.*, *Z. Physiol. Chem.*, 1935, **234**, 196.

[2] Barger, Bergel and Todd, *Ber.*, 1935, **68**, 2257.

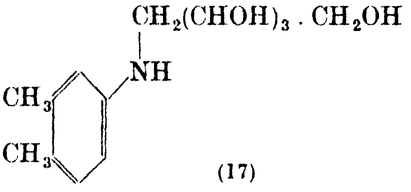
It was suggested that the free flavin of milk was identical with the vitamin B_2 component responsible for growth promotion,[1] as distinct from that component of the so-called B_2, termed the pellagra-preventative (PP-) factor.[2]

The structure of lactoflavin (vitamin B_2) is shown below as 6, 7-dimethyl-9-(*d*-1′-ribityl)*iso*alloxazine (16).



(16)

Although several syntheses have been worked out, that of Karrer and Meerwein [3] is, perhaps, of greatest interest. *o*-4-Xylidine is mixed with *d*-ribose and treated with hydrogen in the presence of palladium, when the compound (17) is obtained, by reduction of the Schiff's base first formed.



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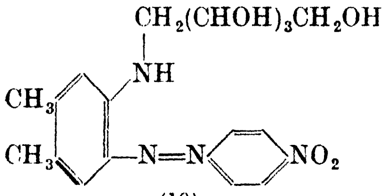
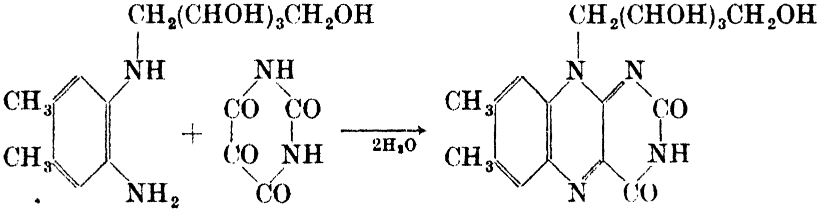


(18)

Diazotised *p*-nitraniline is coupled with this substance in the " 5 " position to give the azo-compound (18), which is reduced to the amine of the structure (19), by hydrogen under pressure in the presence of nickel. The amine readily condenses with alloxan (20) to give lactoflavin (21), a yellow crystalline substance.[4] It has recently been shown that the yield is greater when alloxantin replaces alloxan in the latter condensation.



(19) (20) (21)

Several analogues of lactoflavin have been prepared with different sugar residues, using mannityl, dulcityl, sorbityl, rhamnityl or xylityl groups, but no physiological activity was observed. The *d*-araboflavin has some activity, but the *l*-ribityl derivative has none. It is of importance from the standpoint of structure and activity to note that although the change of *d*- to *l*-ribityl destroys the vitamin B_2 activity, the loss of a methyl group as in 7-methyl-9-*d*-1′-ribityl-isoalloxazine (22) does not. The fact that the compound (22) has a strong vitamin B_2 activity proves that the *o*-xylene structure is not essential for the development of this activity. In addition, in the industrial synthesis of substances of vitamin B_2 activity, a synthesis commencing with *m*-toluidine instead of *o*-4-xylidine is to be preferred. Whether the 7-methyl derivative is the complete physiological equivalent of vitamin B_2 has yet to be determined.

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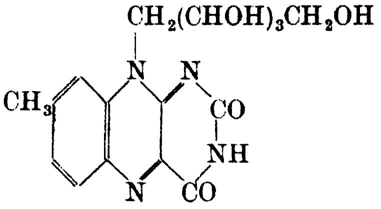
[1] Elvehjem and Koehm, *J. Biol. Chem.*, 1935, **108**, 709.

[2] Karrer *et al.*, *Helv. Chim. Acta.*, 1935, **18**, 908.

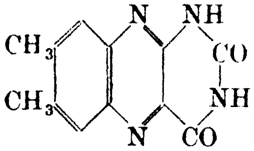
[3] Karrer and Meerwein, *ibid.*, 1935, **18**, 1130.

[4] Karrer and others, *ibid.*, 1935, **18**, 69, 522.



(22)

Vitamin B_2 is extremely sensitive to light and exposure of the solution rapidly removes the ribityl residue leaving 6, 7-dimethyl alloxazine (or lumichrome) (23). In alkaline solution the ribityl group is removed only in part and the residual material is 6, 7, 9-trimethyl alloxazine (lumiflavin) (24).



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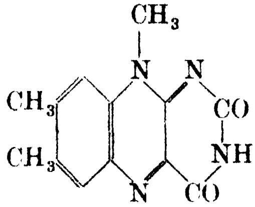

(24)

The yellow respiratory ferment of Warburg [1] is an association of the lactoflavin phosphate with protein. Theorell [2] was able to break down the pigment into protein and flavin phosphate; the parts were without enzyme activity, but on recombining them the activity was restored.

OTHER MEMBERS OF THE VITAMIN B COMPLEX

There have been identified the following additional members of the B complex :—

Pyridoxin
Pantothenic acid
Nicotinic acid
Inositol
p-Aminobenzoic acid
Biotin

of these, three are simple organic substances which have been known for some time: nicotinic acid, inositol and *p*-aminobenzoic acid; their chemistry is discussed in the appropriate place. Information concerning the other three is given below.

PYRIDOXIN

We owe much of our knowledge of pyridoxin (vitamin B_6) to Szent-György who in 1934 noted the existence of a water-soluble factor, distinct from those already known, absence of which in the diet of rats induced dermatoses. It was four years later that the actual vitamin B_6 was isolated [3] in the form of colourless crystals, m. 200-202°. It is soluble in water and alcohol, unaffected by moderate heat, but is decomposed by ultra-violet irradiation.

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[1] Warburg and Christian, *Biochem. Z.*, 1932, **254**, 438 ; 1933, **266**, 377.

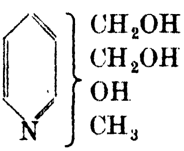
[2] Theorell, *Biochem. Z.*, 1934, **272**, 155 ; 1935, **278**, 263.

[3] Keresztasy and Stevens, *J.A.C.S.*, 1938, **60**, 1267 ; *Proc. Soc. Exp. Biol. Med.*, 1938, **38**, 64 ; Lepkovsky, *J. Biol. Chem.*, 1938, **124**, 125 ; Kuhn and Wendt, *Ber.*, 1938, **71**, 780, 118 and 1534.

Kuhn and his co-workers[1] worked out its structure in 1938–1939. They observed the following points :—

(1) Empirical formula $C_8H_{13}O_3N$.
(2) The following functional groups were characterised :—
  (*a*) Weakly basic tertiary nitrogen.
  (*b*) Two primary alcohol groups.
  (*c*) One phenolic hydroxyl group.
  (*d*) One C-methyl group.
(3) Degradation gave indications of a pyridine ring.

The structure of pyridoxin from these observations may therefore be expressed as (25) and the orientation of the groups has next to be ascertained.



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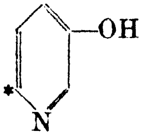

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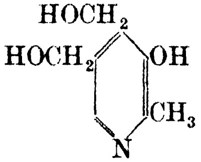
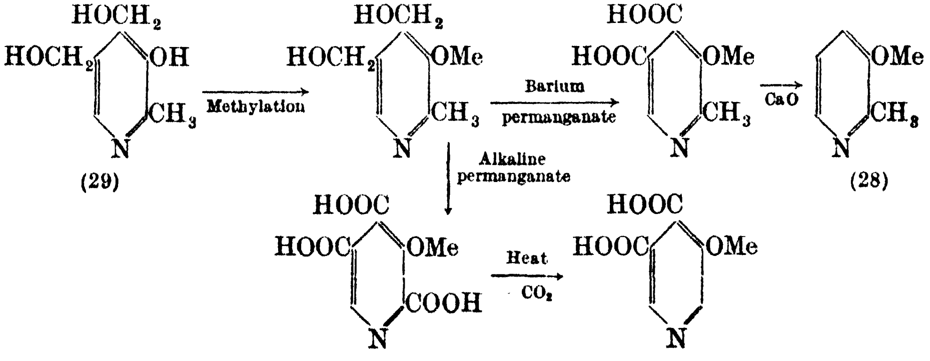


(27)

Examination of the absorption spectrum points definitely to a 3-hydroxy compound, and the fact that it condenses readily with 2, 6-dibromoquinone chlorimide to give a coloured indophenol indicates that the position *para-* to the hydroxyl group is unsubstituted [marked * in (26).][2]

Alkaline permanganate, acting on the methyl ether of pyridoxin, yields a tricarboxylic acid (28*a*) which loses carbon dioxide on heating, a reaction indicative of a pyridine-α-carboxylic acid. This leads to the formation of the dicarboxylic acid (29*a*) ; on the other hand, barium permanganate acting on the



(29) (28) (28*a*) (29*a*)

methyl ether of pyridoxin, oxidises the two primary alcohol groups to carboxyl groups, which (as do those of 29*a*) give a fluorescein reaction and are therefore in adjacent positions ; thus the two original primary alcohol groups must have been in the "4" and "5" positions (27), leaving only the "1" position available for the methyl group. This was confirmed by decarboxylating the dicarboxylic acid over lime when 3-methoxy-α-picoline (28) is obtained. Thus, pyridoxin is 2-methyl-3-hydroxy-4, 5-di-(hydroxymethyl)pyridine (29). The formula has been confirmed by synthesis by two independent routes. In that of Kuhn and his co-workers [1] the methoxy methyl isoquinoline (30) is nitrated, bringing the nitro group into an unspecified position in ring A (31); on reduction to the amine (32) and oxidation the benzenoid ring is destroyed, leaving 1-methyl-2-methoxy-pyridine-3, 4-dicarboxylic acid (33). The next task is to convert the carboxyl groups to CH_2OH, for which purpose a difficult series of operations was carried out involving change of the group to $—CONH_2$, $—CN$, $—CH_2NH_2$, $—CH_2Br$, $—CH_2OH$. These, although conventional changes, are difficult to carry through with good yield. The treatment with concentrated hydrobromic acid required to demethylate the methoxy group, unfortunately converts the $—CH_2OH$ groups to $—CH_2Br$, and an additional step had to be added to convert these groups back again to $—CH_2OH$ with silver acetate.

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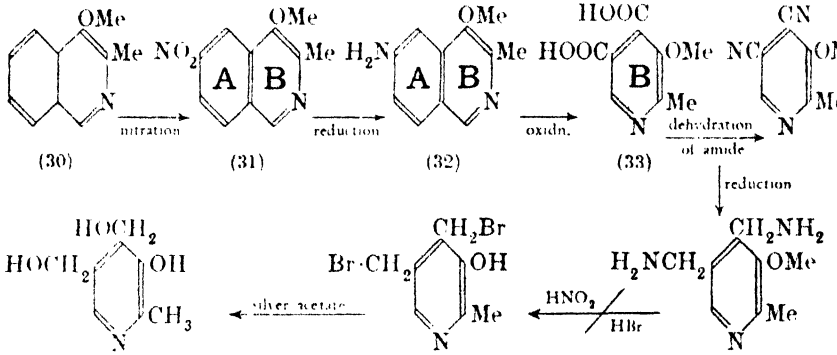
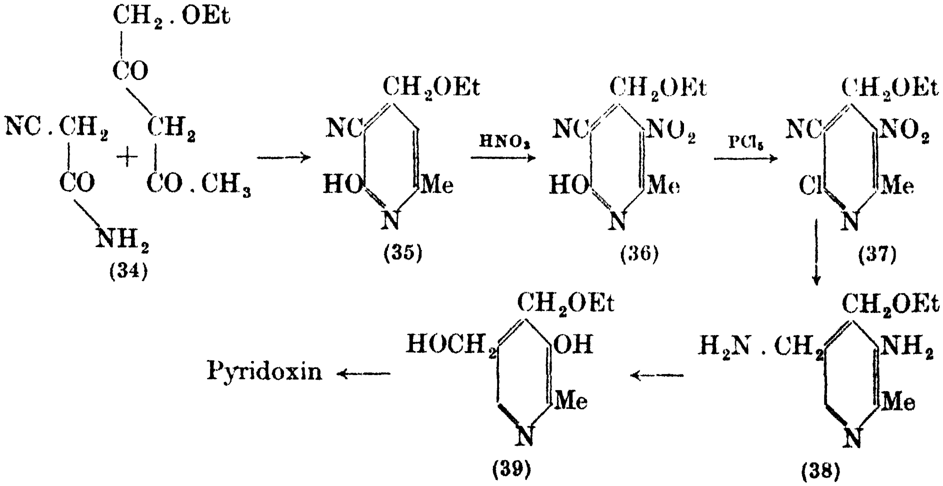
[1] Kuhn, Wendt. *et al.*, *Ber.*, 1938, **71**, 1534 ; 1939, **72**, 305 and 310.
[2] Gibbs, *J. Biol. Chem.*, 1927, **72**, 649.



An alternative method commences [2] with the condensation of 1-ethoxy-pentandione-2, 4 with cyanacetamide (34), whereby a pyridine is obtained with a hydroxyl group in the '6' position (35); by nitration and use of phosphorus pentachloride 3-nitro-2-methyl-5-cyano-6-chloro-4-ethoxymethylpyridine (37) is obtained. Reduction of this compound not only removes the chlorine and reduces the nitro- group to amino, but at the same time converts the $—CN$ group to $—CH_2NH_2$ (38); treatment with nitrous acid yields the monoethyl ether of pyridoxin (39).



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[1] Kuhn *et al.*, *Naturwiss.*, 1939, **27**, 469.

[2] Harris, Stiller and Folkes, *J.A.C.S.*, 1939, **61**, 1237.

PANTOTHENIC ACID

Williams and his co-workers[1] observed a growth-stimulating factor which appeared to be essential for the growth of yeast and many other micro-organisms, and was later[2] shown to be necessary for rats and other animals.

Although the structure of pantothenic acid did not prove difficult to elucidate, the amount available amounted only to a fraction of a gram, so that the successful outcome of the experimental work must be regarded as a brilliant application of microchemical technique. Thus, 3 mg. of pantothenic acid, hydrolysed with dilute hydrochloric acid gave 0·2 mg. of β-alanine which was characterised by a naphthalene sulphonic acid derivative.[3] Since the empirical formula of pantothenic acid was known to be $C_9H_{17}O_5N$ the splitting off of β-alanine may be represented by the equation :—

$$C_9H_{17}O_5N + H_2O \longrightarrow \underset{\beta\text{-alanine}}{H_2N\,.\,CH_2\,.\,CH_2\,.\,COOH} + \underset{\text{Fraction B}}{[C_6H_{12}O_4]} \longrightarrow C_6H_{10}O_3 + H_2O$$

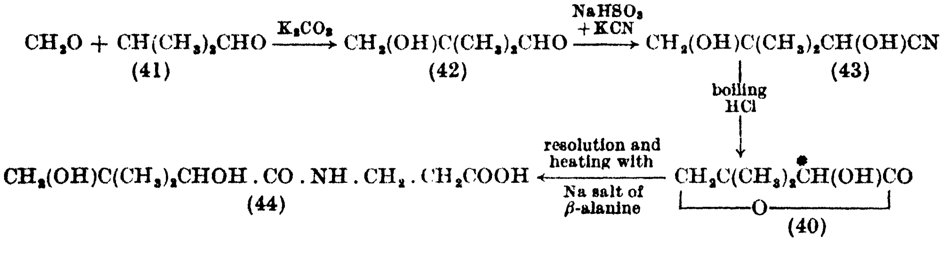
The identity of fraction B proved more difficult to elucidate ; in the first place the substance isolated proved to be a lactone of the formula $C_6H_{10}O_3$, the elements of water having been lost from the formula given in the equation above. Thus, pantothenic acid must have the structure of an acid amide. Fraction B gave carbon monoxide with concentrated sulphuric acid indicating a α-hydroxy acid (α-hydroxy acids decompose thus :

$$R\,.\,CH(OH)COOH \longrightarrow RCHO + CO + H_2O$$

in the presence of strong sulphuric acid). The structure of the original pantothenic acid is, therefore, elucidated so far as :—

$$HO[C_4H_8]\text{—}CH(OH)\,.\,NH\,.\,CH_2\,.\,CH_2\,.\,COOH$$

The nature of the C_4H_8 group was worked out by Williams and Major,[4] who identified it as $\text{—}CH_2C(CH_3)_2\text{—}$. The lactone is, therefore, 3, 3-dimethyl-2-hydroxy-1, 4-epoxybutanone (40), sometimes called α-hydroxy-ββ-dimethyl-γ-butyrolactone).



The synthesis of pantothenic acid has been effected by condensing aqueous formaldehyde with isobutyraldehyde (41) to give 3-hydroxy-2, 2-dimethylpropanal (42) which, in turn, adds on the elements of hydrogen cyanide to give the nitrile (43). This, boiled with hydrochloric acid furnishes the lactone referred to above as ' fraction B '. It will be noted that this lactone contains an asymmetric carbon atom (*) (40) ; the natural lactone is the *l*-isomer, and by fractional crystallisation of the quinine salt of the corresponding acid, the *l*-lactone was obtained.

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[1] Williams *et al.*, *J.A.C.S.*, 1939, **61**, 454.
[2] Subbarow and Hitchings, *ibid.*, 1939, **61**, 1615.
[3] Weinstock, Mitchell, Pratt and Williams, *ibid.*, 1930, **61**, 1421.
[4] Williams and Major, *Science*, 1940, **91**, 246.

The final synthesis was best carried out by heating together the dry lactone and the sodium salt of β-alanine, when pantothenic acid, identical with the natural product, (44) was obtained.

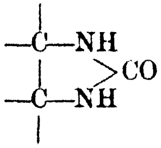
BIOTIN

The term ' bios ' was used to describe a complex of many factors, which appeared to be essential for yeast growth. Of the original ' bios ' group many components—inositol, vitamins B_1 and B_2, pantothenic and p-aminobenzoic acids have already been discussed. Of the remaining factors one of the most important is biotin, a growth factor which appears to be not only essential for plant and animal growth but to play a fundamentally important part in cell physiology. It resembles the auxins (*q.v.*) in the minuteness of the quantities required for its effect. Kögl[1], in 1932, commenced a series of researches on the nature of the ' bios ' associated with yeast growth. By adsorption onto charcoal and stripping with acetone-ammonia, biotin was finally isolated. Kögl isolated it in crystalline form and György[2] demonstrated its identity with the so-called vitamin H, m. 230–231° ; $[\alpha]_D^{25°} = 92°$, the curative factor for egg-white injury.

Biotin appears to be the most biologically active substance yet discovered, since it still shows its characteristic behaviour at a dilution of 1 in 4×10^{11}. It is widely, albeit very sparingly, distributed ; to obtain 1 gram, 350 tons of ordinary yeast would have to be treated—and Kögl and his co-workers spent five years in obtaining 70 mg. of crystalline methyl ester, the empirical formula of which is $C_{11}H_{18}O_3N_2S$.

The following essential features were observed concerning the structure of biotin :—

(1) It gave carbon dioxide and a diamine on hydrolysis. The diamine regenerated the original biotin on treatment with phosgene (indicating the presence of a urea group in biotin) and gave quinoxaline derivatives with o-quinones implying an o-diamine structure. It must, therefore, contain the group



$$\begin{array}{l} \;\;\mid \\ -\mathrm{C}-\mathrm{NH} \\ \;\;\mid \qquad \gt \mathrm{CO} \\ -\mathrm{C}-\mathrm{NH} \\ \;\;\mid \end{array}$$

(2) The diamine referred to above gave adipic acid on oxidation, indicating the possibility of a $—(CH_2)_4COOH$ side-chain.

(3) By a modified Hofman reaction a δ (α-thienyl) valeric acid was obtained the structure of which was confirmed by synthesis.

(4) The nature of the sulphur in biotin was largely revealed by the action of cold permanganate, which oxidised biotin to a sulphone ; the same, very stable, product is obtained by oxidation of biotin with hydrogen peroxide in acetic acid.

(5) Raney nickel has been successfully used to eliminate the sulphur of biotin (cf. Bouganet in the cleavage of disulphides), yielding a desthiobiotin (45*a*), which was hydrolysed by concentrated baryta to 7, 8-diamino pelargonic acid (45*b*), the quinoxaline from which (45*c*) was shown to be identical with that from the synthetic acid.

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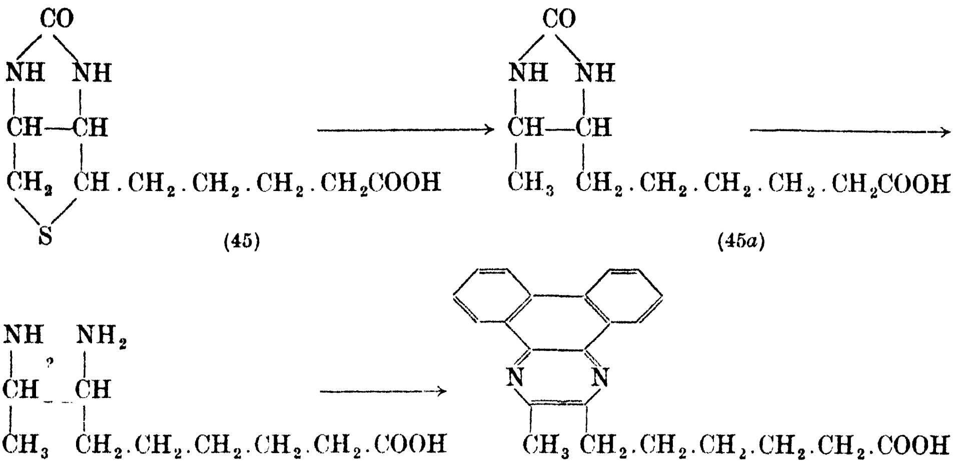
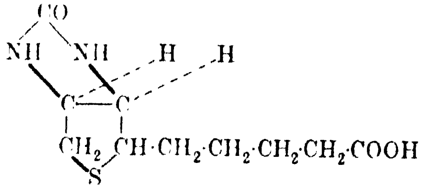
[1] Kögl and Tönnis, *Z. physiol. Chem.*, 1936, **242**, 43.

[2] György *et al.*, *Science*, 1940, **91**, 243.

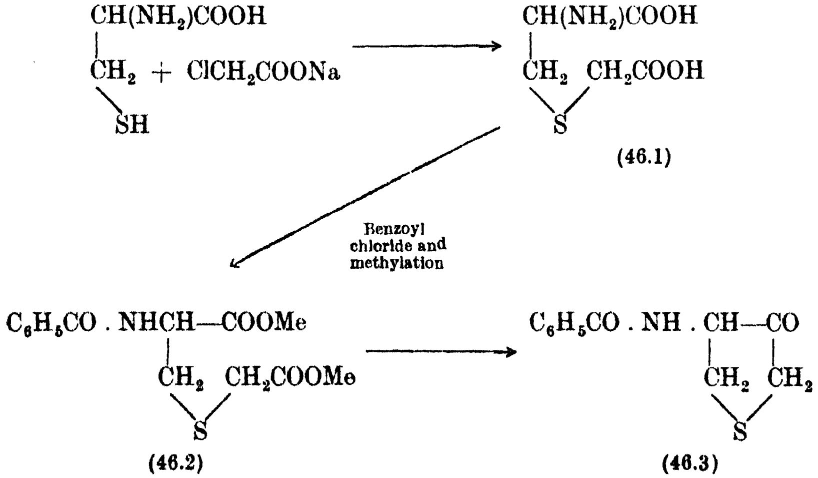

(45) (45a) (45b) (45c)

The structure which these above data suggests, and which has been proved by synthesis to be correct,[1] is (45), 2′-keto-3, 4-imidazolidothiophane-2-valeric acid. The stereochemical implications of the three asymmetric carbon atoms are somewhat modified by the strong tendency which all fused ring compounds with two five-membered rings possess to form *cis-* forms (46) in preference to *trans-*, the latter being almost unknown.


(46)

The synthesis of biotin takes the following course :—

(1) Cysteine is allowed to react with an alkaline solution of sodium monochloroacetate :—



(46.1) (46.2) (46.3)

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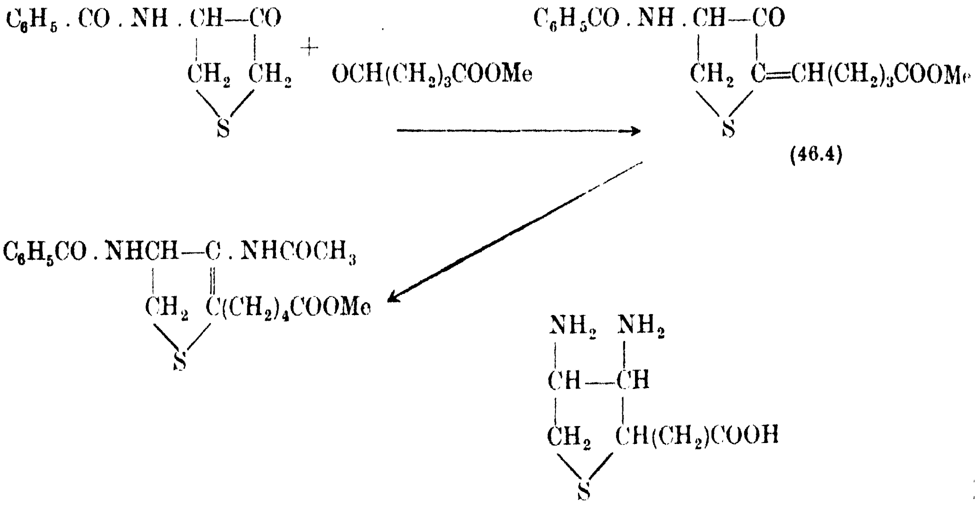
[1] Harris *et al.*, *Science*, 1943, **97**, 448 ; *J.A.C.S.*, 1944, **66**, 1756.

(2) The thioether (46.1) obtained in Stage I is benzoylated at the amino group, and both carboxyl groups are methylated (46.2).
(3) Heating with sodium methoxide causes (46.2) to suffer ring closure, giving the thiophenone derivative (46.3).
(4) The side chain is next attached by condensing (46.3) with the methyl ester of the half-aldehyde of glutaric acid, resulting in the compound (46.4), the oxime of which on reduction with zinc dust, and a mixture of acetic acid and acetic anhydride yields (46.5).



(46.4)

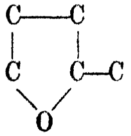
(46.5) (46.6)

(5) The double bond of (46.5) can be reduced with hydrogen and palladium, and the two acyl groups removed by successive treatment with baryta and sulphuric acid which also restores the free carboxyl group. The product of this stage is (46.6).
(6) The diamine (46.6) is converted to β-biotin by phosgene.

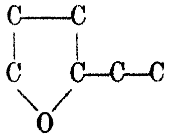
VITAMIN C

Szent-Györgyi[1] in 1928 isolated a compound $C_6H_8O_6$ from oranges, from cabbage, and from the cortex of the adrenal gland. This substance, crystalline, and having a high antiscorbutic effect, was called "hexuronic acid", but since later work showed it not to be a member of the uronic acid series, it was renamed "*l*-ascorbic acid". Later *l*-ascorbic acid was shown to be identical with vitamin C, the well-recognised antiscorbutic factor.

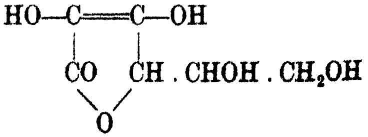
Chemically, the structure of *l*-ascorbic acid is comparatively simple, and was elucidated by Haworth, Hirst and others[2]; the fact that it gives furaldehyde



(47)



(48)



(49)

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[1] Szent-Györgyi, *Biochem. J.*, 1928, **22**, 1387; 1932, **26**, 865.

[2] Haworth, *Chemistry and Industry*, 1933, **52**, 482; Hirst, *ibid.*, 1933, **52**, 221; Hirst *et al.*, *J.C.S.*, 1933, 1270; H. v. Euler and C. Martius, *Svenske, Vet. Akad. f. Kemi, etc.*, 1933, **B11**, No. 14.

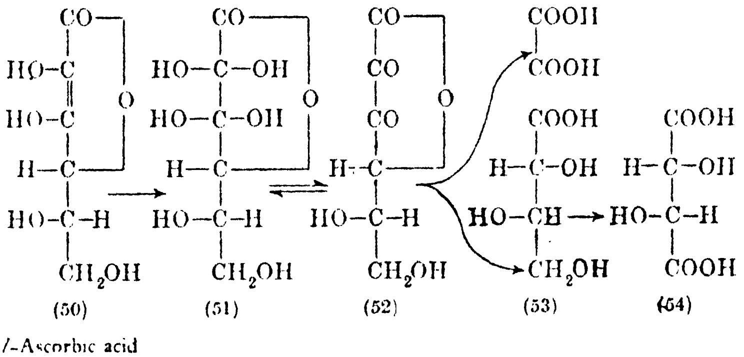
quantitatively on boiling with hydrochloric acid indicates a skeleton (47) and the absence of other substituents further indicate that the remaining carbon atom is in the side-chain (48).

The reducing power of *l*-ascorbic acid, its ability to undergo reversible oxidation, to react with iodine and to show acidic properties, led to the suggestion that the seat of its activity and acidity resided, not in a carboxyl group, but in a dissociating hydroxyl group, probably of the type —C(OH)=C(OH)— already familiar from studies of dihydroxymaleic acid. The existence of a double bond can be demonstrated by reaction with diazomethane.

When oxidised with iodine, a substance is obtained having the properties of a lactone ; if *l*-ascorbic acid is both a lactone and contains the

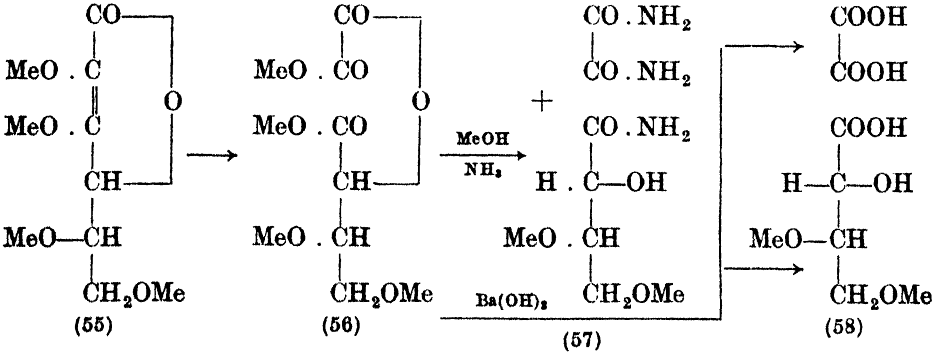
—C(OH)═C(OH)—

group, its formula must be (49), since there is only one place for the lactonic carbonyl group in the structure (48), and when this is taken, only one possible situation for the —C(OH)═C(OH)— group. This relation is more clearly elucidated from the more conventional representation of *l*-ascorbic acid (50).



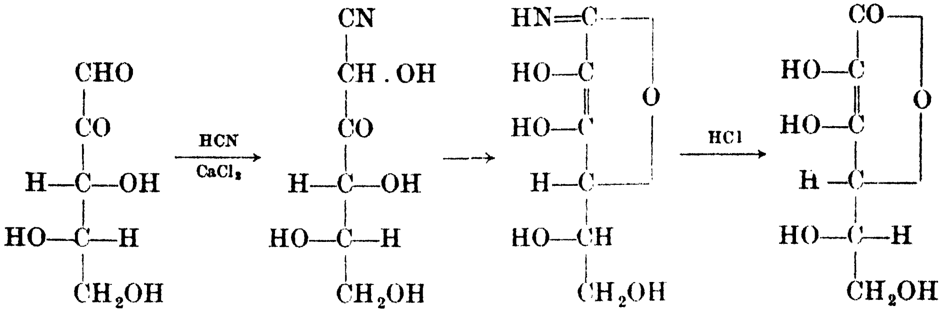
Further oxidation of the product (51) or (52) (obtained by the action of iodine on *l*-ascorbic acid) with sodium hypoiodite gives quantitatively oxalic and *l*-threonic acids (53), the latter's identity being confirmed by conversion to the crystalline trimethyl-*l*-threonamide and by oxidation to *d*-tartaric acid (54).

Much additional evidence has been accumulated to confirm the conclusions described above. The main evidence is obtained from the breakdown of tetramethyl-*l*-ascorbic acid (55).



Ozone attacks the double-bond of tetramethyl-*l*-ascorbic acid, giving the neutral substance (56) which is hydrolysed by ammonia in methanol to oxamide and 3, 4-dimethylthreonamide (57), and by baryta to oxalic and 3, 4-dimethylthreonic acids (58).

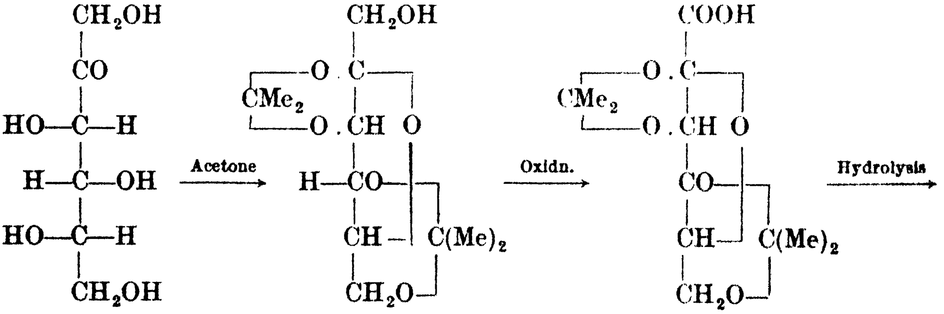
Final confirmation was given by synthesis, by Reichstein and co-workers,[1] and by workers in this country. An important step in the development was the synthesis of Haworth,[2] Hirst and others in which *l*-xylosone (59) was prepared and



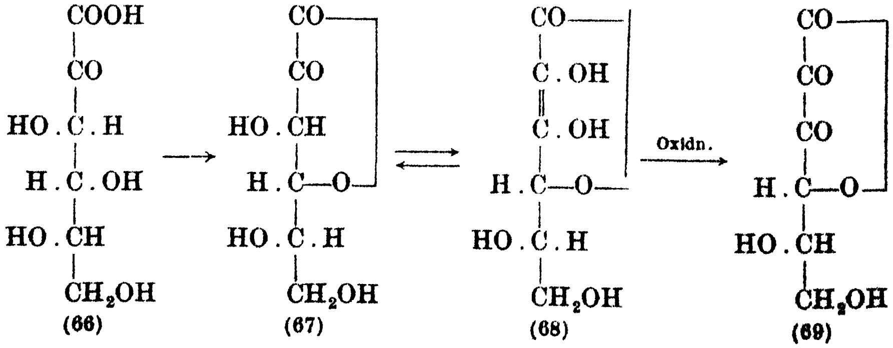
(59) (60) (61) (62)

characterised ; converted by a mixture of $CaCl_2$ and KCN to the nitrile (60) which changes immediately to the imino-compound (61). This substance has some antiscorbutic properties, but it is by no means as active as the lactone (62) (vitamin C) into which it may be converted by hydrochloric acid. *l*-Ascorbic acid crystallises in white needles. It may be added that this work of Haworth and his co-workers constitutes the first synthesis of a vitamin ; Reichstein *et al.* obtained only the acetone derivative of inactive *d*-ascorbic acid.

The industrial synthesis commences with sorbitol, which is bacterially oxidised to *l*-sorbose (63) by *Acetobacter xylinum*. This is converted to its di-acetone compound (64) and oxidised to the carboxylic acid (65), the acetone



(63) (64) (65)



(66) (67) (68) (69)

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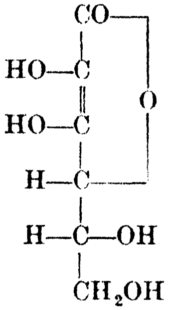
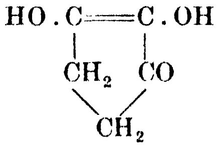
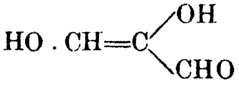
[1] Reichstein, Grüssner and Oppenauer, *Helv. Chim. Acta.*, 1933, **16**, 561, 1019.
[2] Haworth and Hirst, *Chem. and Ind.*, 1933, **52**, 645 ; *et al.*, *J.C.S.*, 1934, **1192**.

residues being stripped by acid hydrolysis. This gives 2-keto-L-gulonic acid (66) the lactone of which is tautomeric with ascorbic acid, and is converted to it (68) by boiling with dilute acid in an inert atmosphere. The presence of air leads to oxidation to the less active dehydroascorbic acid (69).

The biochemical nature of its function is not known with certainty—it is certain, however, that small differences in structure destroy the activity. *d*-Ascorbic acid has no antiscorbutic activity in doses forty times as great as those used with *l*-ascorbic acid, and the so-called " *iso*vitamin C " (70) has only 1/20-1/50th of the activity of *l*-ascorbic acid.


(70)


(70*a*)


(70*b*)

There are two related substances of great biochemical interest, namely, reductive acid, etc., and reductone (70*b*). Both contain the 'enediol' system of ascorbic acid, but their biochemical function is, as yet, imperfectly known.

Citrin or Vitamin P

In 1936, Szent-Györgyi [1] arrived at the conclusion that the full antiscorbutic activity of paprika and lemon-juice was not entirely realised by the administration of ascorbic acid, and that the syndrome of scurvy was produced by the joint deficiency of two vitamins—vitamin C and a new vitamin, vitamin P, to which the name " citrin " has also been given. This has been confirmed by the work of Bacharach and his co-workers.[2]

The complete identity of vitamin P is obscure; Szent-Györgyi isolated citrin, a mixed crystal of the glycosides of hesperitin and eriodictyol, but according to Bacharach and his co-workers [2] the activity of pure hesperidin (hesperitin glycoside) is less than one-hundredth part of that of a water-soluble concentrate from blackcurrants. The chemistry of the glycosides of this family has already been dealt with in Appendix III to Chapter V.

Vitamin E

That there existed an anti-sterility vitamin E [3] has been known since 1922, when it was demonstrated that on synthetic diets (containing all the vitamins of which the investigators were aware at that date) female rats had failed, after normal mating, to bring their pregnancy to a satisfactory termination.[4] The first rich source of this material was to be found in the unsaponifiable matter of wheat germ oil.[5] Since then the vitamin has been found in the unsaponifiable matter of many vegetable oils, in nearly all seed germs and in lettuce.

---

[1] Szent-Györgyi *et al.*, *Deut. med. Woch.*, 1936, **62**, 1325 *Nature*, 1936, **138**, 27, 138, 1057; 1936, **138**, 798; *Z. Physiol. Chem.*, 1938, **225**, 126.

[2] Bacharach, Coates and Middleton, *Chem. and Ind.*, 1942, **61**, 96.

[3] Evans and Bishop, *Science*, 1922, **56**, 650; Mattill, *J. Biol. Chem.*, 1922, **50**, 44.

[4] Mattill and Stone, *ibid.*, 1923, **55**, 443; B. Sure, *ibid.*, 1924, **58**, 693.

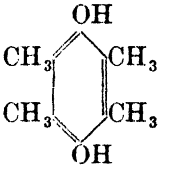
[5] Evans and Burr, *Mem. Univ. Calif.*, 1927, No. 8.

By the use of allophanic esters Evans and the Emersons[1] were enabled to isolate two alcohols, α- and β-tocopherol, both of which had that activity which had previously been associated with vitamin E concentrates. Later[2] a third substance, γ-tocopherol, was isolated from cottonseed-oil. The alcohols themselves are rather difficult to handle and purify, and their separation has been carried out mainly by their esters with the acids 3, 5-dinitrobenzoic and allophanic ($NH_2 . CO . NH . COOH$) and by the conversion of the alcohols to 4-nitrophenyl urethanes. The empirical formulæ of the tocopherols has been established as follows :—

α-tocopherol . $C_{29}H_{50}O_2$
β-tocopherol . $C_{28}H_{48}O_2$
γ-tocopherol . $C_{28}H_{48}O_2$

Thus the β and γ forms appeared to be isomeric and to be lower homologues of the α-tocopherol.

Work on the constitution of these two substances was initiated by Fernholz[3] and by McArthur and Watson,[4] who showed that on pyrolysis or degradation with selenium, α-tocopherol gave duroquinol (71) ; similarly, the β-analogue was found to be capable of conversion to ψ-cumoquinol (72) by a similar sequence of reactions. Thus the position of the extra methylene group in α-tocopherol was settled and the structural problem remaining to be settled was the nature of the group removed during degradation.



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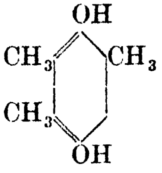
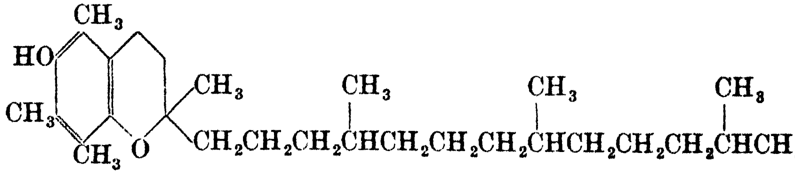


(72)

Whilst it was tempting to regard the structure of the tocopherols as ethers of the quinols formed by their degradation, Todd and his co-workers pointed out that this hypothesis was untenable and that synthetic long chain alkyl ethers of duroquinol had no relation to the tocopherols either chemically, physically or biologically. They suggested[5] a coumaran or chroman structure, as also did Karrer and his co-workers[6] and Fernholz[7] and, since it was becoming evident that the long chain was the phytyl group, the following tentative structure was put forward :—



(73)

The brilliant synthetic work of Karrer and others[8] confirmed the authenticity of this suggested structure. They condensed phytylbromide and ψ-cumoquinol (74) in petroleum ether using anhydrous zinc chloride as a condensing agent and obtained a racemic α-tocopherol (73).

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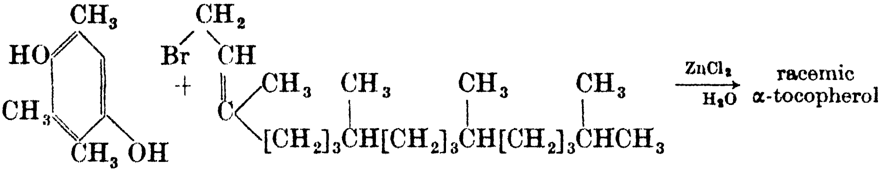
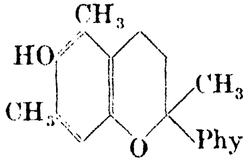
[1] Evans, O. H. Emerson and G. H. Emerson, *J. Biol. Chem.*, 1936, **118**, 319.
[2] *Idem.*, *Science*, 1936, **83**, 421.
[3] Fernholz, *J.A.C.S.*, 1937, **59**, 1054.
[4] McArthur and Watson, *Science*, 1937, **86**, 35.
[5] Bergel, Todd and work, *J.C.S.*, 1938, 253.
[6] Karrer *et al.*, *Helv. Chim. Acta*, 1938, **21**, 309.
[7] Fernholz, *J.A.C.S.*, 1938, **60**, 700.
[8] Karrer *et al.*, *Helv. Chim. Acta*, 1938, **21**, 520 and 820.



(74)

This material was resolved through the bromocamphorsulphonate to a product identical with natural tocopherol. The possibility of the formation of a coumaran, not a chroman, structure is not excluded by this method of synthesis, but all the evidence of properties, absorption spectra and analogy lead to the confirmation of the chroman ring.

With the β and γ-tocopherols the ambiguities are greater ; the *o*-, *m*- and *p*-xyloquinols can all be made to give compounds similar to that from ψ-cumoquinol. The three isomers are :—



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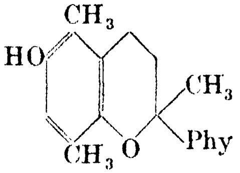

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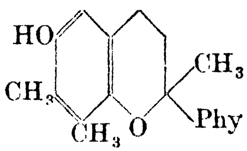


(77)

It is not known with certainty which of these is β- and γ-tocopherol, but (76) is thought to be the β-compound and (77) to be the γ-form.

The way in which vitamin E works is obscure, and its consideration from this angle is outside the scope of this book. It is clear, however, that its presence is essential to both male and female for efficient reproduction, and that it plays a part in maintaining the general muscular tone of the growing child.

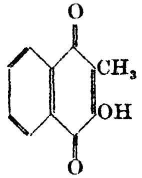
VITAMIN K

The biochemistry of this vitamin differs somewhat from that of others in that a number of simple substances, some of which bear no chemical relation to the vitamin itself, are capable of exerting a very similar activity. The origin of work on vitamin K (' K ' from ' Koagulations-vitamin ') lies in the observations of Dam and Schönheyder [1] that certain deficiency conditions of chicks resembling scurvy and showing also a marked diminution of blood-clotting, could not be cured by ascorbic acid, but needed a new and hitherto unrecognised nutritional factor to which the term vitamin K was applied. This vitamin has been found in liver, cereals, vegetables, e.g., spinach and chestnut leaves, certain bacteria,[2] e.g., *B. subtilis* and *Staph. aureus*, alfalfa meal and putrified fish-meal.

It soon became obvious that several closely related natural substances showed K activity, one of which was the yellow substance, phthiocol, isolated from tubercle bacilli.[3] Phthiocol is 2-methyl-3-hydroxy-1, 4-naphthoquinone (78) and its biological similarity to the K vitamins has played a considerable part in the development of this subject. Two K vitamins were first isolated, vitamin K_1, from alfalfa, and vitamin K_2 from putrified fish-meal. The former is a yellow oil, and the latter a yellow crystalline solid, m. 54° ; both are 3-substituted derivatives of β-methyl-naphthoquinone, K_1 the phytyl derivative (79), and K_2 the derivative of a highly unsaturated chain. In the formulæ below the structure of these compounds is written to illustrate the relation of the phytyl chain to the terpene and vitamin A family (it is not contended that the carbons are spatially arranged as in these illustrations).

---

[1] Dam, *Biochem. Zeitschr.*, 1930, **220**, 158 ; *Nature*, 1934, **133**, 909 ; 1935, **135**, 652.
[2] Butt and Snell, *J. Nutrition* (Suppl.), 1938, **15**, 11.
[3] Almquist and Klose, *J.A.C.S.*, 1939, **61**, 1611.



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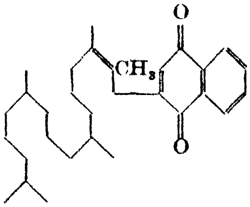
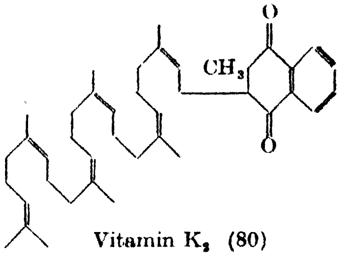


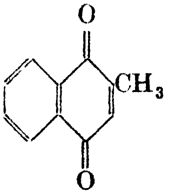
Vitamin K_1 (79)



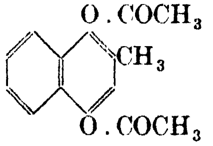
Vitamin K_2 (80)

The synthesis of vitamin K_1 was effected by the condensation of phytylbromide and 2-methyl-1, 4-naphthoquinone.[1]

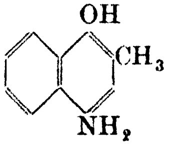
It has been established that the physiological activity of these naphthoquinone derivatives is not impaired if the long side-chain in the ' 3 ' position is removed. Thus, simple compounds such as 2-methyl-1, 4-naphthoquinone (81) have a strong K activity, and are widely used in medicine for this purpose.



(81)



(82)



(83)

Thus, the methylnaphthoquinone just mentioned is distributed under the official name ' Menaphthone '. Its insoluble nature makes it unsuitable for oral administration, for which purpose acetomenaphthone (2-methylnaphthohydroquinone diacetate) (82) is used, or the so-called vitamin K_5, 4-amino-2-methyl-1-naphthol (83). The comparative values of the various substances discussed above is shown in the table below :—

		Dam units
Vitamin K_3	Phthiocol	10–60
Vitamin K_2	— [See (80)]	8,000
Vitamin K_1	2-Methyl-3-phytyl-1, 4-naphthoquinone	12,000
Acetomenaphthone	2-Methyl-1, 4-naphthoquinol diacetate	14,000
—	2-Methyl-1, 4-naphthoquinol disuccinate	15,000
—	2-Methyl-1, 4-naphthoquinol diphosphoric ester (Na salt)	25,000
Vitamin K_3 (Menaphthone)	2-Methyl-1, 4-naphthoquinone	25,000
Vitamin K_5	4-Amino-2-methyl-1-naphthol	30,000

---

[1] Almquist and Klose, *J.A.C.S.*, 1939, **61**, 2537 ; Fieser, *J.A.C.S.*, 1939, **61**, 2559.

THE HORMONES

It has already been mentioned that minute traces of chemical substances are synthesised in the ductless glands of the animal system for biochemical purposes, mainly for regulating the various metabolic and reproductory processes. Their biochemical significance cannot be over-estimated, but chemically only a small portion have, as yet, yielded the secrets of their structure. Of these, adrenaline, from the adrenal gland, is discussed in Chapter XI of Vol. II, in connexion with the ephedra alkaloids, with which it shows chemical similarity; thyroxin is discussed below; and the sex hormones and those from the adrenal cortex in their appropriate place among the steroids (p. 905).

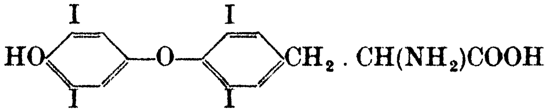
There is little to be obtained by discussing in detail those hormones whose structure is not yet elucidated; the hormones of the anterior and posterior pituitary; the active hæmopœitic principles of liver and stomach-wall; hormones of the hypophysis, the parathyroids; insulin, if it is permissible to include this substance as a hormone; all these are essential to life and health and the elucidation of their structure offers a field of enquiry for the modern organic chemist.

THYROXIN

In 1833, Kocher [1] showed that a relation existed between goitre and the thyroid gland, and two years later, Roos [2] prepared a concentrated extract of the gland. Similar substances prepared by Oswald [3] in 1900 received the name of thyreoglobulin. Nürenberg [4] (1909) demonstrated the iodo-protein nature of part of the concentrate, and obtained positive reactions for tyrosine and tryptophane among the products of hydrolysis.

Kendall [5] in 1915 first isolated the active principle, thyroxin, and when, in 1919, about 33 gm. of thyroxin had been isolated, Kendall proposed for it a structure —4 : 5 : 6-trihydro-4 : 5 : 6-triodo-2-oxy-β-indolepropionic acid.

Harington [6] (1926) improved the method of extraction, and showed that Kendall's proposals were incorrect, and by a careful study of the breakdown products arrived at the formula (84) for thyroxin, and subsequently confirmed this by synthesis.



(84)

Harington established the empirical formula of thyroxin as $C_{15}H_{11}O_4NI_4$, and was successful in obtaining, by the action of palladium and hydrogen, a desiodothyroxin $C_{15}H_{15}O_4N$, in which the structure of thyroxin itself is preserved intact. Desiodothyroxin had all the properties of an α-amino acid, and on caustic fusion at 250° gave *p*-hydroxybenzoic acid, hydroquinone and a compound $C_{13}H_{12}O_2$; by fusions conducted in an atmosphere of hydrogen, ammonia, oxalic acid, hydroquinone and *p*-hydroxybenzoic acid were isolated, from which the formula

$$HO . C_6H_4[C_6H_4O]CH_2 . CH(NH_2)COOH$$

may be deduced.

---

[1] Kocher, *Arch. Klin. Chir.*, 1883, **29**, 254.

[2] Roos, *Z. Physiol. Chem.*, 1895, **21**, 19.

[3] Oswald, *ibid.*, 1901, **32**, 121.

[4] Nürenberg, *Biochem. Z.*, 1909, **16**, 87.

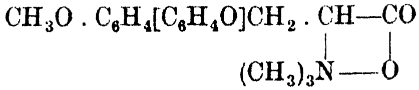
[5] Kendall, *J. Am. Med. Assoc.*, 1915, **64**, 2042; *J. Biol. Chem.*, 1919, **39**, 125.

[6] Harmeton, *Biochem. J.*, 1929, **20**, 293, 300; Harington and Barger, *Biochem. J.*, 1927, **21**, 169.

When desiodothyroxin is methylated, a betaine is obtained which gives the following series of reactions :—

$$HO\,.\,C_6H_4[C_6H_4O]CH_2\,.\,CH(NH_2)COOH$$

$$\Big\downarrow\ \text{Exhaustive methylation}$$



$$\begin{array}{l} CH_3O\,.\,C_6H_4[C_6H_4O]CH_2\,.\,CH—CO \\ \qquad\qquad\qquad\qquad\qquad\ \ | \qquad\ | \\ \qquad\qquad\qquad\qquad (CH_3)_3N—O \end{array}$$

$$\Big\downarrow\ \text{boiling alkali}$$

$$CH_3OC_6H_4[C_6H_4O]CH{=}CH\,.\,COOH + N(CH_3)_3$$

$$\Big\downarrow\ \text{Oxidation}$$

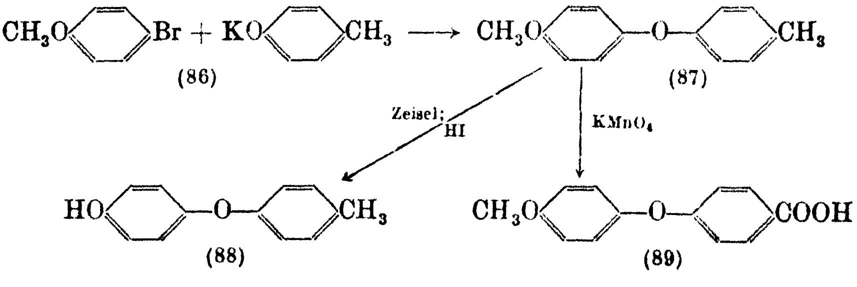
$$CH_3OC_6H_4[C_6H_4O]CHO$$

$$\text{Further}\ \Big\downarrow\ \text{oxidation}$$

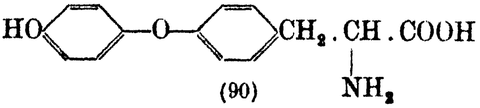
$$CH_3OC_6H_4[C_6H_4O]COOH$$

(85)

Each step of this degradation was followed by ultimate analysis and characterisation of the functional group, and the acid (85) was synthesised as follows. *p*-Bromoanisole and the potassium salt of *p*-cresol (86) condense in the presence of copper bronze to give 4-methyl-4′-methoxy diphenyl ether (87), which, by Zeisel's method gives the corresponding hydroxy derivative (88). This proved to be the compound $C_{13}H_{12}O_2$ obtained during the caustic fusion of desiodothyroxin. By permanganate oxidation of the 4-methyl-4′-methoxydiphenyl ether (87), the acid (89) was obtained identical with that (85), resulting from the degradation of methylated desiodothyroxin.



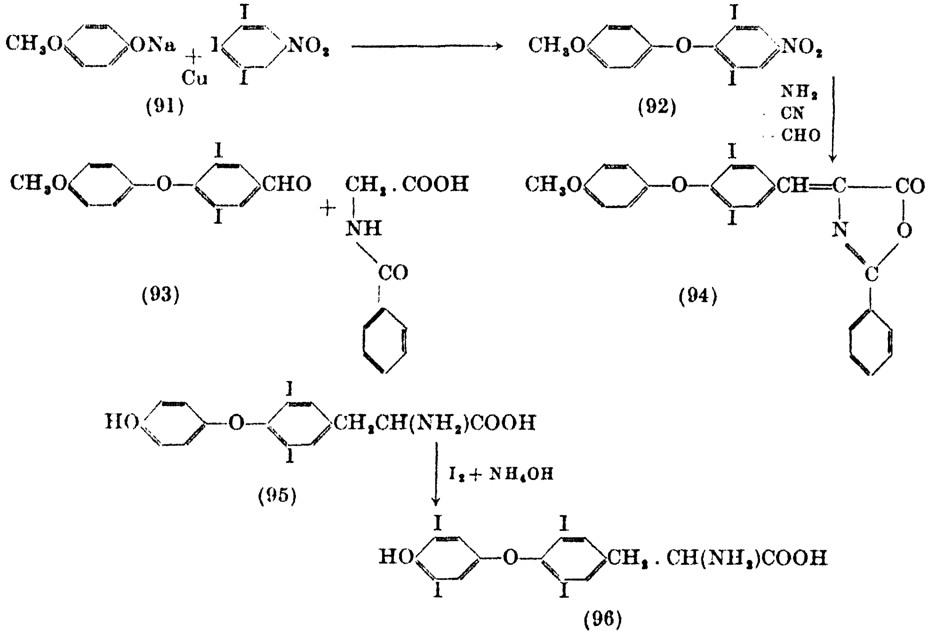
(86) (87) (88) (89)



(90)

The structure of desiodothyroxin is, therefore, given by (90) ; the position of the four iodine atoms of thyroxin itself was suggested (from the many possible isomers) by analogy with iodogorgonic acid (3, 5-diiodotyrosine) and was confirmed by synthesis. Iodogorgonic acid has itself been isolated from thyreoglobulin, but was obtained independently from corals (*Gorgonia cavolini*), and from sponges. It is present in iodinated casein hydrolysates, and may be obtained synthetically by the iodination of tyrosine.

Harington's synthesis is carried out by allowing the sodium salt of hydroquinone monomethyl ether (91) to react with 3, 4, 5-triiodonitrobenzene in the presence of copper bronze, when 4-methoxy-2′, 6′-diiodo-4′-nitrodiphenyl ether (92) is obtained. The nitro group of this compound is reduced to an amino group, replaced by —CN, using Sandmeyer's method and converted to the —CHO group by reduction with stannous chloride in moist ether.



An azlactone (94) is produced when the aldehyde (93) is condensed with hippuric acid; reduction of the azlactone with phosphorus and iodine yields the diiodo compound (95) which, with iodine in ammoniacal solution, yields *dl*-thyroxin (96). It may be added that the product so obtained is identical with that obtained from natural sources, since racemisation takes place during extraction of the natural material. The racemic form can be resolved, but active *d*- and *l*-thyroxine are more easily obtained by carrying out the resolution on compound (95), followed by iodination. The *l*-form is considerably more active biologically than the *d*-form. At the present moment it is doubtful whether the synthetic material is more cheaply obtainable than that from natural sources.

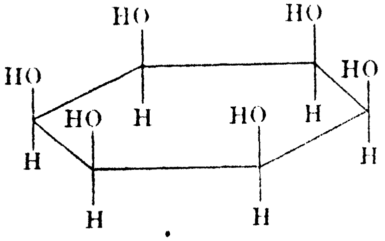
THE PHYTOHORMONES

In the early days of vitamin and hormone knowledge, the two groups were considered separately, but time has shown them to be members of a large group of substances drawn from many forms of biological material, and necessary for the continuance of vital processes. Amongst these, phytohormones stand revealed as an important group of growth accessory substances essential to vegetable life.

Until 1901, the conception of plant nutrition as laid down by Pasteur was universally accepted; namely that plants (yeast in particular) require for nutrition only water, inorganic salts and fermentable sugars. In 1901, Wildiers inoculated washed yeast cells into such a medium and failed to obtain growth or fermentation; only when wort or similar substances had been added did growth and fermentation commence. Wildiers traced the effect to the presence in the wort of a thermo-stable substance which appeared to be an accessory growth factor for yeast; he gave it the name of ' bios '.

Subsequent work showed that different forms or micro-organisms required different substances, and that ' bios ' was not a universal phytohormone, but could be regarded as a generic name for a large group of substances, the members of which are not necessarily related chemically. Thus, Lash Miller and Eastcott showed that for certain types of growth *meso*-inositol acted as a ' bios ' factor ; Williams and others in U.S.A. showed that for certain strains of yeast a ' bios ' factor is vitamin B_1, and it has since been shown that this factor is responsible for growth stimulation in germinating rice, for which purpose it is stored in the aleurone cell layer of the rice grain. The structure of vitamin B_1 has already been discussed.

The inositols are the cyclic hexahydric alcohols of general formula $C_6H_6(OH)_6$ (cyclohexan-hexa-ol). The stereoisomers of inositol are shown in the following table, in which reference is made to (97) where the ring is assumed to be in a horizontal plane with the hydroxyl groups either above or below.



(97)

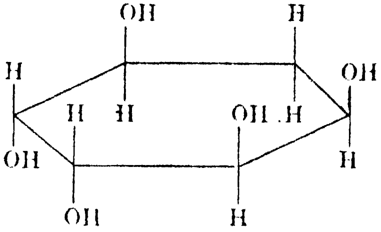
TABLE I

Number of OH groups below ring	Position of "upper" hydroxyl groups	Occurrence
0	—	
1	Any	The *meso*- or *i*-inositol ; ' bios ' (Lash Miller) ; commonly occurring in muscle and plant tissues
2	(*a*) 1 : 2 (ortho) (*b*) 1 : 3 (meta) (*c*) 1 : 4 (para)	
3	(*a*) 1 : 2 : 3 (vicinal) (*b*) 1 : 2 : 4 (unsymmetrical) (*c*) 1 : 3 : 5 (symmetrical)	* (See below)

The unsymmetrical inositol (1 : 2 : 4 inositol) marked above with an asterisk is capable of existing in dextro and lævo forms, since its molecule has no element of symmetry. This was one of the earliest examples of compounds whose optical activity is due to asymmetry of the molecule rather than to the simple asymmetry of a carbon atom.

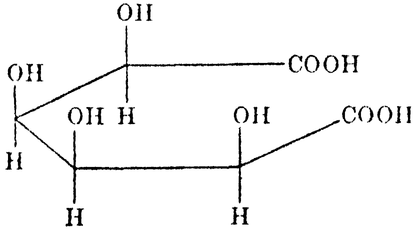
The ordinary or *meso*-inositol is prepared from the phytin of unripe peas ; phytin is the calcium or magnesium salt of inositol hexaphosphoric ester, and may be hydrolysed to the free hydroxyl compound by heating with dilute sulphuric acid at 140°. Inositol compounds are widely distributed in nature, both as the free base and as the phosphoric esters. The methyl derivatives are well-known ; pinitol is monomethyl-*d*-inositol and quebrachitol is the corresponding methyl-*l*-inositol ; scyllitol is an inositol of undetermined structure from the organs of elasmobranch fish. It may also be mentioned that *d*-quercitol (a pentahydroxy cyclohexane) is also well distributed in nature, but its biological significance is not clear.

The configurations of quercitol and *meso*-inositol have been worked out by oxidation. Quercitol yields mucic acid (HOOC + — — + COOH), malonic acid, and *b*-trihydroxyglutaric acid (HOOC + — — COOH), and is optically active, from which it is deduced that the structure of quercitol is (98) :—

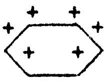


(98)

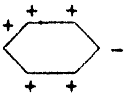
Similarly, *meso*-inositol gives allomucic acid (HOOC + + + + COOH) (99), on oxidation from which it can be seen that *meso*-inositol itself must be of the



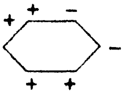
(99)



(100)



(101)



(102)

form (100), (101) or (102). Since the monophosphoric ester cannot be resolved optically, formula (102) is excluded ; and the general properties of the substance point to the structure (101) which is the accepted configuration. Apparently biotin, vitamin B_1 and *meso*-inositol work together since growth proceeds in the presence of all three to a considerable extent, but is minimal in the presence of any one singly. Other substances which have been found to exert a specific influence on plant growth are nicotinic acid, *β*-alanine, *l*-leucine and pantothenic acid, together with the so-called auxins.

THE AUXINS

The auxins are concerned with cell elongation in plant growth, and are formed in the tips of growing shoots from which they move by diffusion to the lower parts. Hence, if the tip of a growing shoot is sliced off, growth stops temporarily, but may be restarted by placing on the stump a tiny block of agar jelly, containing a minute amount of auxin. Thus, if, in Fig. V, *A* represents the normal growth of a shoot, *B* indicates the cessation of growth on slicing off the top ; *C* shows the renewed growth proceeding with the artificial supply of auxin maintained by the agar block. In *D* the result of placing the agar block unsymmetrically on the stump is shown ; one side grows but the other does not, thus leading to curvature. Using oat shoots (*Avena sativa*), the quantity of phytohormone which, under standard conditions, will produce a curvature equivalent to $\theta = 10°$ is termed the ' avena unit '. Auxin-a has about 5×10^{10} avena units per gram.

During the years 1931–1936 Kögl and others isolated crystalline auxins from a great variety of natural materials, urine, excreta of herbivorous animals, maize, oil, malt and yeast. Three auxins were found [1]—auxin-a ($C_{18}H_{32}O_5$) and auxin-b ($C_{18}H_{30}O_4$), obviously closely related, and hetero-auxin, a substance containing nitrogen and identical with β-indolyl acetic acid previously quite well known. Since the discovery of the phytohormone activity of indolyl acetic acid, attention has been focussed on a variety of substituted acetic acids derived from benzene, naphthalene, anthracene, etc., many of which exert a profound stimulant action on root formation, a property of which advantage has been taken industrially. Kögl was able to demonstrate a considerable difference between the stimulant activities of *d*- and *l*- forms of α-(β′indolyl)-propionic acid which is indicated below :—

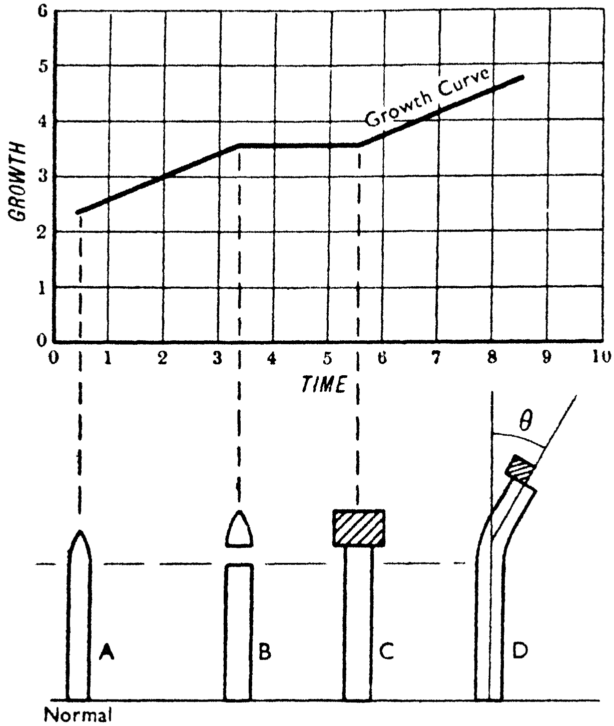
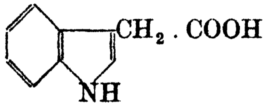


Fig. V.



	Activity.
Racemic acid . . .	23 × 10^9 A.U./gm.
Dextro ,, . . .	1·6 × A.U./gm.
Lævo ,, . . .	48 × 10^9 A.U./gm.

Chemical Structure of the Auxins

The elucidation of the structures of auxin-a and auxin-b is a triumph of the application of micro-analysis and micro-manipulation ; most experiments were carried out on quantities of a few milligrams, from which in many cases two or more compounds were isolated, purified, analysed and identified. Kögl and his co-workers used only 700 mg. in all in establishing the structure of auxin-a. There is little doubt that many major advances into the study of naturally occurring biochemical products will, in future, depend largely on micro-technique, for the development of which organic chemists owe a debt of gratitude to Pregl, who became interested in the subject of micro-analysis through a study of the bile-acids ; in one series of reactions dealing with a degradation of a bile-acid he obtained so minute a yield, that he decided to develop a technique of microanalysis rather than repeat the preparative work on a larger scale.

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[1] Kögl *et al.*, *Z. Physiol. Chem.*, 1934, **225**, 228.

The method of extraction of auxin-a from human urine was as follows : 150 litres of urine gave 87 gm. of an ether extract from which acids were removed by washing with sodium bicarbonate solution, and fats by special extractions with petroleum ether and ligroin. The residual 20 gm. of material gave, by a series of extractions, 2·25 gm. of solid crude auxin, and vacuum distillation separated 0·04 gm. of a comparatively pure product which, by crystallisation, gave the auxin-a readily convertible to the auxin-a lactone.

Auxin-a has the following properties :—

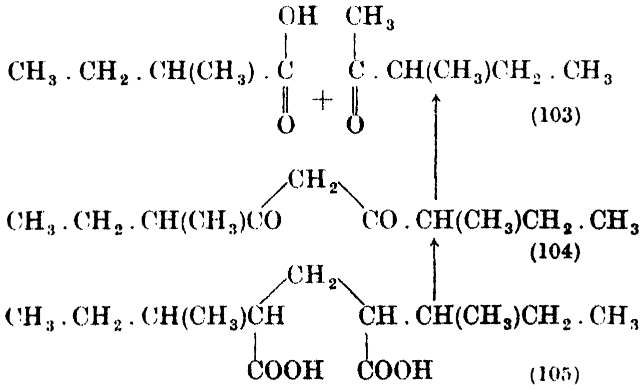
1. It is a white crystalline substance having the empirical formula $C_{18}H_{32}O_5$ and a molecular weight of 328.
2. It readily forms a lactone, and must therefore have a hydroxyl group attached to a carbon chain terminating in —COOH. There are three hydroxyl groups in all.
3. Auxin-a has a single double-bond.
4. Computation of the hydrogen :—

Actually present . .	32
Allowance for —COOH .	2
,, ,, double-bond	2
	36

   shows two short of the 38 required for an open chain compound, indicating one carbocyclic ring.

5. Auxin-b gives similar results, save that whereas auxin-a has three hydroxyl groups, auxin-b has two hydroxyl and one keto-group.

When auxin-a or auxin-b is oxidised with permanganate or ozone, an auxin-glutaric acid ($C_{13}H_{24}O_4$) is obtained which, by further oxidation, is converted to a diketone $C_{11}H_{20}O_2$. This compound has the characteristic properties of a β-diketone, and by fission with potassium hydroxide yields α-methylbutyric acid and 3-methylpentan-2-one (103) from which the reconstruction of the β-diketone (104) can be formulated thus :—



$$CH_3 . CH_2 . CH(CH_3) . \underset{O}{\overset{OH}{C}} + \underset{O}{\overset{CH_3}{C}} . CH(CH_3)CH_2 . CH_3$$

(103)

$$CH_3 . CH_2 . CH(CH_3)CO \overset{CH_2}{\quad} CO . CH(CH_3)CH_2 . CH_3$$

(104)

$$CH_3 . CH_2 . CH(CH_3)\underset{COOH}{CH} \overset{CH_2}{\quad} \underset{COOH}{CH} . CH(CH_3)CH_2 . CH_3$$

(105)

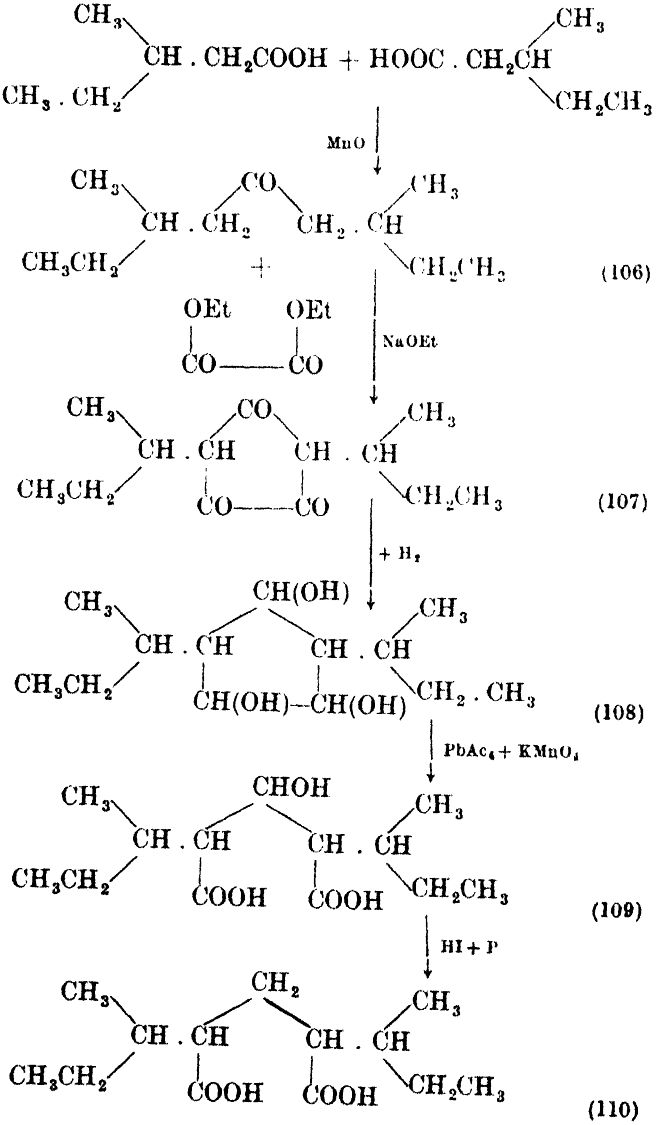
and since the two ketonic groups must mark the original point of attachment of the carboxyl groups, auxin glutaric acid must have the structure (105). This has been confirmed by synthesis.[1]

---

[1] Kögl, *Chem. and Ind.*, 1938, pp. 49–54.

SYNTHESIS OF AUXIN-GLUTARIC ACID

A di-*iso*amyl ketone (3, 7-dimethylnonan-one-5) (106) was obtained by distilling *d*-*sec*-butylacetic acid over manganous oxide; this ketone condensed with ethyl oxalate in the presence of sodium ethoxide to give a di-*iso*-butylcyclopentantrione (107), which was reduced by nascent hydrogen to the corresponding tri-ol (108). The opening of the ring at the glycol structure and consequent oxidation to dicarboxylic acid (109) was achieved by lead tetra-acetate and potassium permanganate. The compound so obtained differed from auxin-glutaric acid only by the presence of a hydroxyl group, which was reduced to hydrogen by hydriodic acid and phosphorus, thus giving auxin-glutaric acid (110).



(106)

(107)

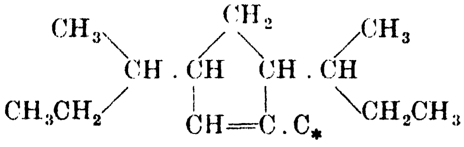
(108)

(109)

(110)

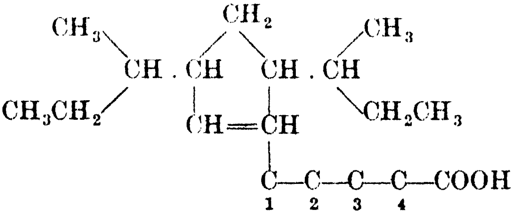
By starting with an active *sec*-butylacetic acid, Erxleben and Michaelis were able to eliminate many of the possible active forms of auxin-glutaric acid, but, even so, more than 300 crystallisations of the cinchonidine salt were necessary before separation of the correct optical isomer was attained. The auxin-glutaric acid so obtained was identical with that obtained from natural sources.

Since auxin-glutaric acid is produced by the oxidation of auxin-a, it is reasonable to suppose that the oxidative attack took place at the site of the double bond, and that auxin-a and auxin-b are derived from the fragment (111) the remainder of the molecule being joined through the carbon atom (*).

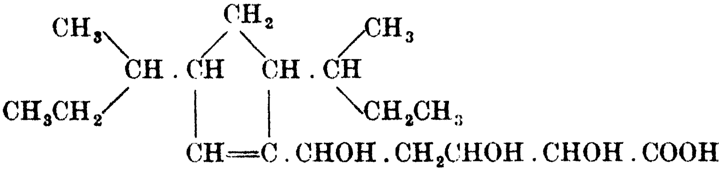


(111)

Since no branched chain fragments have been identified in the breakdown of the side-chain, it is reasonable to suppose that the side-chain is a straight one terminating in the —COOH group. The tentative carbon skeleton of this side-chain is shown in (112). It must be to this side-chain that the three hydroxyl groups are attached; hence, of the four groups between the —COOH and the ring, three are —CH(OH) and one is —CH_2; it is highly improbable that the —CH_2 group is adjacent to the ring, since oxidation would then lead to a ketonic monobasic acid.



(112)

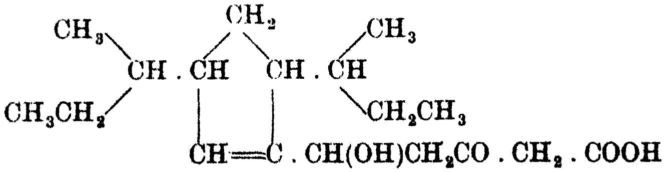


(113)

When dihydroauxin is oxidised, glyoxylic acid and a hydroxy aldehyde are obtained; they could only arise from a side-chain containing a glycol group

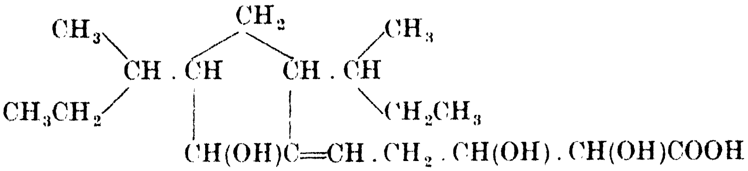
$$\begin{array}{l} \text{—CHOH . CH}_2\text{CHOH . CHOH . COOH} \\ \downarrow \\ \text{—CHOH . CH}_2\text{CHO + CHO . COOH} \end{array}$$

which, therefore, indicates the nature of the side-chain of auxin-a (113). Auxin-b probably has the structure (114)



(114)

Attempts at the complete synthesis of the auxins are fraught with two major difficulties. In the first place, auxin-a has seven asymmetric carbon atoms, and can exist, therefore, as 128 stereoisomers (64 pairs); the use of the correct enantiomorph of auxin glutaric acid would, of course, eliminate some of these, but the task of obtaining the optically correct side-chain is still a formidable one. The second difficulty lies in the fact that both auxin-a and auxin-b change slowly to pseudo-auxins of the structure (115)



(115)

where the isomerisation through the reversal of the allyl group is comparable with that obtained with simpler compounds.

The True Sterols

A few years ago, the sterols and related compounds presented a picture which could only be likened to the unorientated fragments of a jig-saw puzzle; since then, with the elucidation of the structures of the sterols, bile-acids and sex hormones, many pieces of the puzzle have been fitted together, and although the picture is not yet complete, enough has been done to show the relations and harmonies of its main portions.

The presence of the complex alcohol cholesterol in animal tissues has been known for some time, and for many years it has been usual to estimate the amount of this material in blood for purposes of clinical diagnosis. It is only recently, however, that the structure of cholesterol and the sterols has been known with any degree of certainty. Sterols are universally distributed throughout living matter, and in chemical separations tend to accumulate in the unsaponifiable matter of fats, from which they are isolated industrially. Although the sterols crystallise very readily, they form mixed crystals with great ease, and the complete separation of a mixture of two or more sterols by crystallisation is often a matter of extreme difficulty. Sterols form insoluble digitonides, and dibromides which may be used for separation where simple physical methods fail.

The three most widely studied members of the sterol series are cholesterol, $C_{27}H_{46}O$, found in animal cells, especially those of the brain and spinal cord; ergosterol, $C_{28}H_{44}O$ from yeast (derivating its name, however, from ergot, from which it was originally separated) and stigmasterol, $C_{29}H_{48}O$ from the soya-bean. It should be added that the term 'phytosterol' is correctly applied as a general term for a sterol of vegetable origin, and does not represent a homogeneous individual sterol; zoosterol is a generic term applied to sterols of animal origin, and mycosterol for those found in yeasts and fungi.

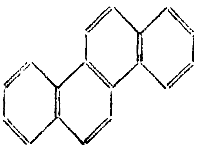
Structure of Sterols

Chemically the sterols exhibit the properties of secondary alcohols, being oxidised to ketones without loss of carbon. The empirical formulæ of the commoner members are given on the opposite page.

It is not within the scope of this book to treat chronologically the data obtained during attempts to elucidate the structure of the sterols. The following points, however, are selected for their fundamental significance.

Chrysene (116) has long been known as a degradation product of cholane derivatives and in 1932 Rosenheim and King suggested that the sterols might be normal derivatives of chrysene, and not, as previously supposed, derivatives of a *bis*-cyclopentanodecahydronaphthalene. It was shown, however, by both Rosenheim and King, and Wieland and Dane, that the cyclopentenophenanthrene (117) nucleus is in full accord with the properties of the steroids, and

Name	Formula	M.P.	Occurrence
Cholesterol	$C_{27}H_{46}O$	150–151°	All animal structures
Ergosterol	$C_{28}H_{44}O$	163°	Yeast, ergot
Spinasterol (α-)	$C_{28}H_{46}O$	172°	Spinach
Coprosterol	$C_{27}H_{48}O$	100–101°	Feces
Ostreasterol	$C_{29}H_{48}O$	142–143°	Shell-fish
Fucosterol	$C_{29}H_{48}O$	124°	Seaweed
Stigmasterol	$C_{29}H_{48}O$	169–170°	Soya beans
Sitosterol (γ-)	$C_{29}H_{50}O$	146°	Plants
Lanosterol	$C_{30}H_{50}O$	141°	Wool fat (Lanolin)



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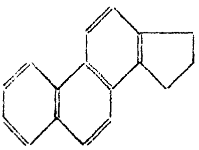

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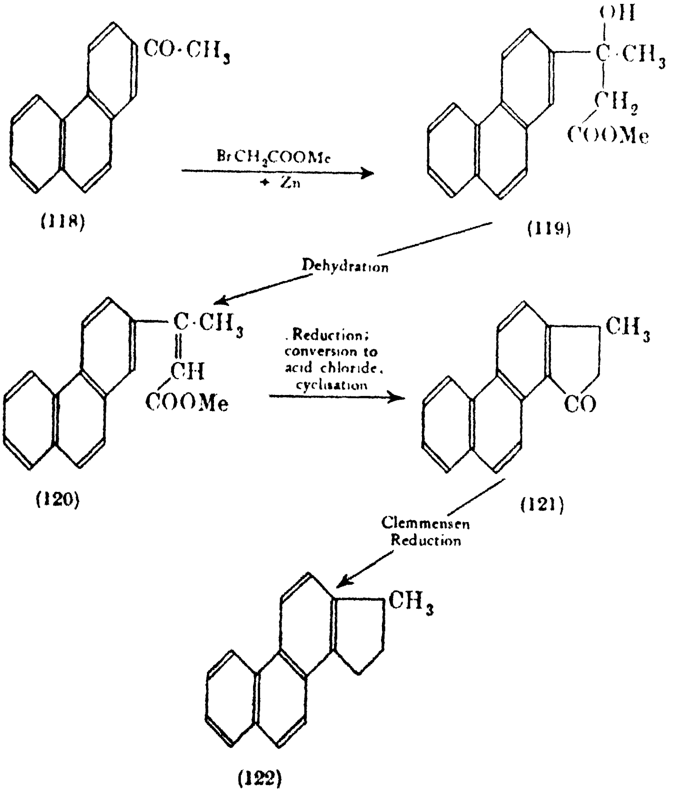
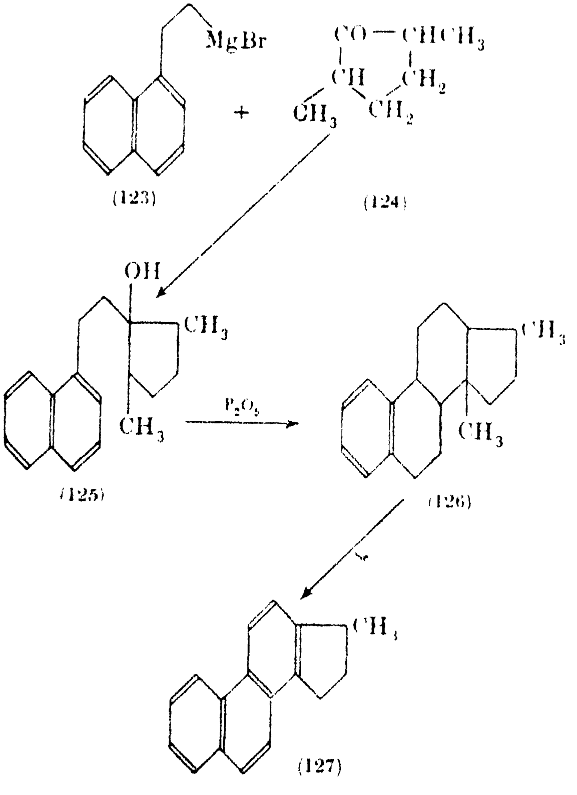


that in all probability, chrysene is produced during their decomposition by a series of intramolecular changes.

The Diels Hydrocarbon.—Dehydrogenation of sterols or allied substances almost always lead to the formation of a certain quantity of hydrocarbon ($C_{18}H_{16}$). The regularity with which this hydrocarbon appears, and its distinctive properties have led to considerable investigation concerning it, and its formula has been established as 3′-methyl-1, 2-cyclopentenophenanthrene (122) both by degradation and synthesis; in addition, other members of the series have been obtained.

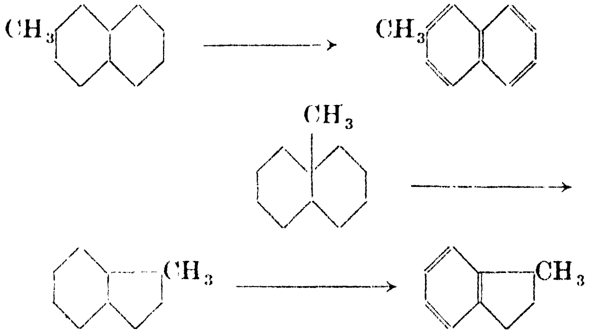
Bergmann and Hillemann's synthesis of the Diels hydrocarbon commenced with 2-acetylphenanthrene (118), which undergoes the Reformatsky reaction with bromacetic ester and zinc in the usual manner to give (119), and, after



dehydration, the unsaturated ester (120). This is reduced with sodium amalgam and converted through the acid chloride to the cyclic ketone (121); reduction of the latter by Clemmensen's method gave 3′methylcyclopentenophenanthrene (122). Difficulty was experienced in identifying this compound with the hydrocarbon from the sterols, and an alternative synthesis giving a purer compound was devised by Harper, Kon and F. C. J. Ruzicka; β-(1-naphthyl)ethyl magnesium bromide (123) was condensed with 2, 5-dimethylcyclopentanone (124) to give the carbinol (125).

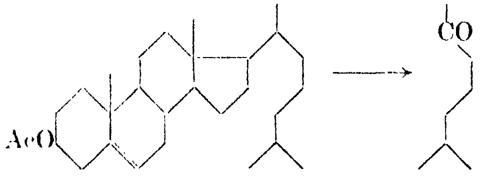
Dehydration of this carbinol led to ring-closure, a dimethylcyclopentanohydrophenanthrene being obtained (126). This gave Diels hydrocarbon (127) on dehydrogenation with selenium.

The use of selenium for the dehydrogenation of cyclic compounds represents one of the more recent advances in the technique of organic chemistry. It is governed by the following general rules; the dehydrogenation of a six-membered ring is usually complete, as also is that of an assemblage of such groups. On the other hand, five-membered rings are usually only dehydrogenated insofar as they are fused to six-membered rings; angular methyl groups are stripped from the nucleus, and appear as volatile alkyl selenium compounds; non-angular methyl groups are unaffected by selenium dehydrogenation. Thus, β-methyldecahydronaphthalene would yield methylnaphthalene; angular-methyldecahydronaphthalene would yield naphthalene, and β-methylhydrindene would be obtained from the corresponding hexahydro derivative—



All known sterols are derived from the cyclopentenophenanthrene nucleus.

The Nature of the Side-chain.—Windaus showed in 1913 that when cholesteryl acetate (128) is oxidised, 2-methylheptanone-6 (129) is obtained; since cholesterol is not itself a ketone, the =CO group of this ketone represents

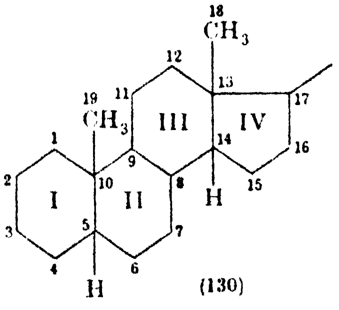


(128) (129)

the point of attachment to the main nucleus, and thus establishes the nature of the side-chain. The reaction is a general one, and serves to characterise the side-chain of many sterols; thus, ergostenol yields an optically active thujaketone, $CH_3CO . CH_2 . CH_2 . CH(CH_3)CH . (CH_3)_2$; cholestanol gives isohexylmethyl ketone. If unsaturation is present in the side-chain, fracture of the side-chain into two portions is usual; ergosterol gives methyl*iso*propylacetaldehyde, and stigmasterol the corresponding ethyl derivative.

Elucidation of the position of double bond and angular methyl groups was only possible after considerable work had been carried out on the bile acids, some of which is described below.

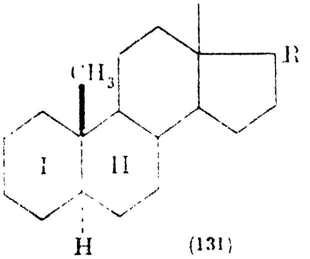
In studying the steroids, considerable experimental difficulties were met.



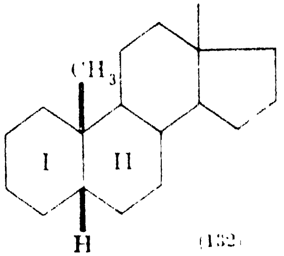
(130)

Firstly, stereochemical problems have proved complex, since the two lower rings I and II of the structure (130) which occur in the majority of the compounds show the *cis-trans* isomerism met with in decalin, and the other rings should be capable of similar geometrical forms ; further, since in the majority of cases, a hydroxyl group is present at " 3 ", this enhances the complexity of the stereo-chemical problem, whilst an asymmetric carbon atom in the aliphatic side-chain attached at " 17 " usually complicates matters still further.

The whole position may be defined by considering the substances obtained by complete reduction of cholesterol ; according to the means used for carrying out this reduction two substances may be obtained, cholestane and coprostane which are *trans-* and *cis-* isomers (referred to rings I and II) of the following type (131) and (132).

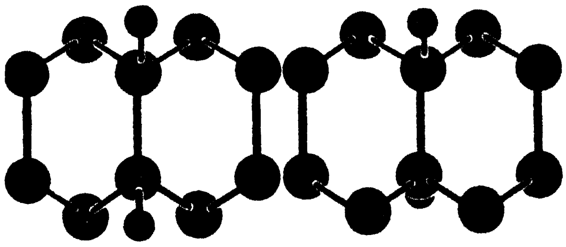


(131)
Cholestane (*Trans*)



(132)
Coprostane (*Cis*)

In these formulæ, the rings are assumed to lie in the plane of the paper ; groups joined by thick lines are above the plane, and those by broken lines below the plane. This isomerism is comparable exactly to that of *cis-* and *trans-* decalin as shown in the figure below :—

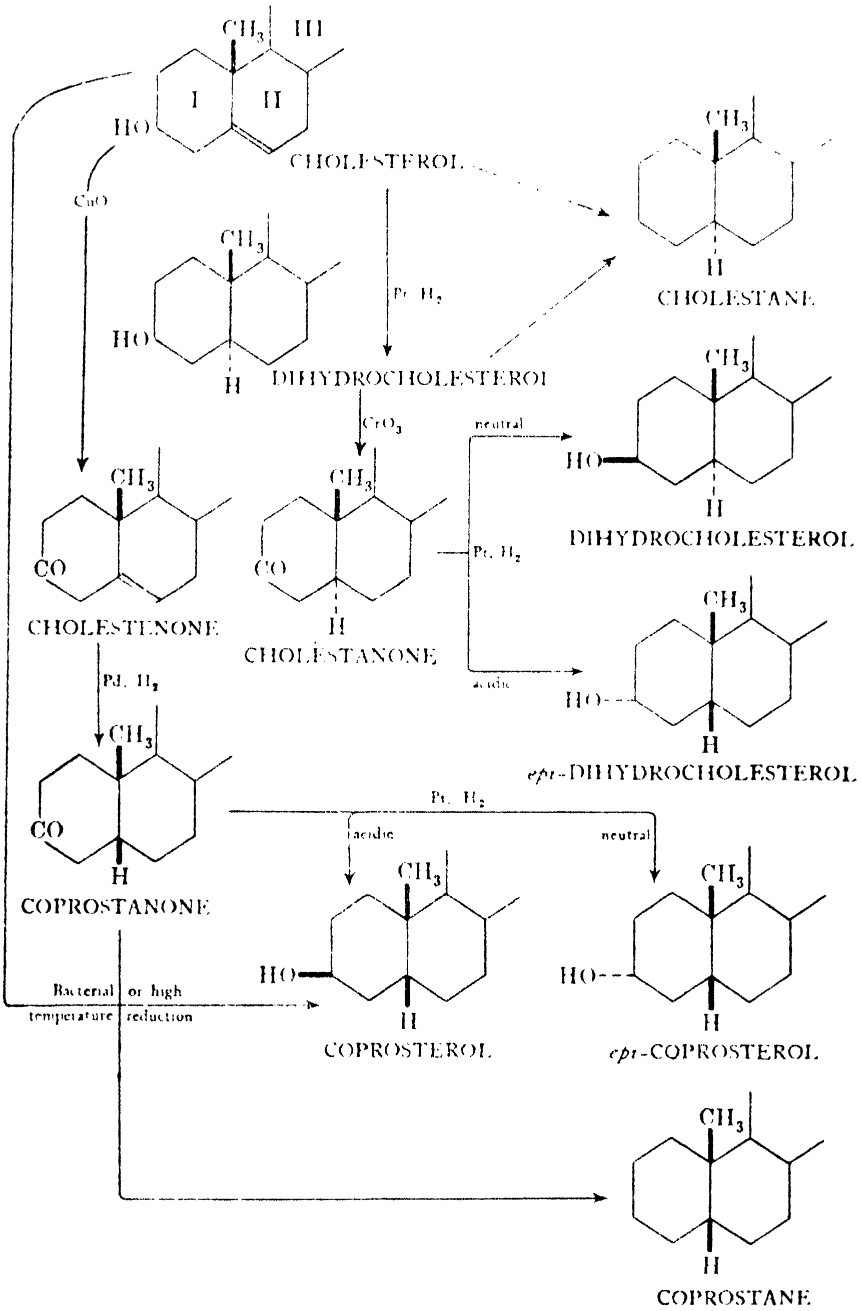


cis- trans-

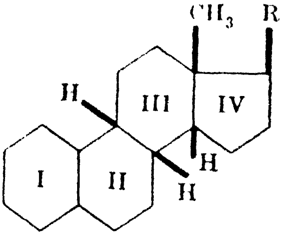
The scheme outlined in Table II below indicates the interrelations between the various reduction products in so far as rings I and II are concerned ; direct reduction of cholesterol by vigorous means gives cholestane ; less vigorous measures give dihydrocholesterol from which the cholestanone and cholestanols may be obtained ; on the other hand, copper oxide converts cholesterol to a cholestenone which is, by virtue of its freedom from potential isomerism the common link between the two series ; suitable reduction of the cholestenone gives coprostanone and coprostane.

So far, no consideration has been given to other centres of geometrical asymmetry in the sterol structure. It is clear the rings III and IV should be capable of giving rise to stereoisomeric forms (133) at each of the thick bonds leading to an 8-fold multiplication of the isomerism already discussed. There is no complete information regarding the stereochemical arrangements in these rings, but the general conclusion is drawn that it does not differ among the commoner sterols and their derivatives, and that in the case of II/III and

TABLE II


CH3 III
I II
HO
CHOLESTEROL
CuO
Pt H2
HO
H DIHYDROCHOLESTEROL
CHOLESTANE
CrO3
neutral
HO
DIHYDROCHOLESTEROL
CO
CHOLESTENONE
CO
CHOLESTANONE
Pt, H2
acidic
epi-DIHYDROCHOLESTEROL
Pd, H2
CO
COPROSTANONE
Pt, H2
acidic
neutral
HO
COPROSTEROL
HO
epi-COPROSTEROL
Bacterial or high temperature reduction
COPROSTANE

III/IV ring junctions it is *trans*-. Thus, if we take a full view of the steric possibilities of the sterols, we find that it is related to dihydrocholesterol and coprosterol, and that the configurations of the four main root-substances are



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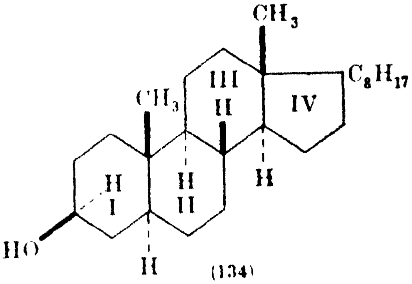


(134)

expressed in the Table III. As far as we are aware, no change of the II/III and III/IV configuration occurs in natural products and in the compounds

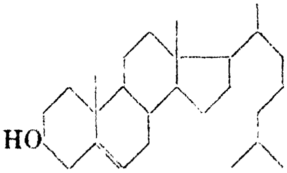
TABLE III

CONFIGURATIONS

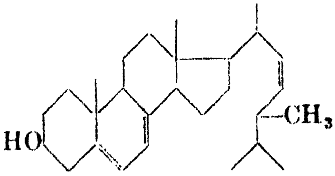
Name	HO/H at 3	I/II ring	II/III ring	III/IV ring
Dihydrocholesterol . .	trans	trans	trans	trans
Coprosterol . . .	cis	cis	trans	trans
epi-Dihydrocholesterol .	cis	trans	trans	trans
epi-Coprosterol . .	trans	cis	trans	trans

subsequently discussed these factors are ignored. Cholesterol has eight asymmetric carbon atoms, so that numerous optical isomers are possible—many of which are known.

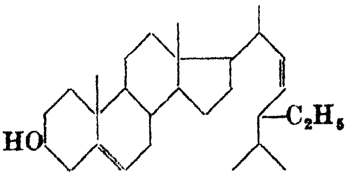
The four most widely distributed sterols are usually formulated :—



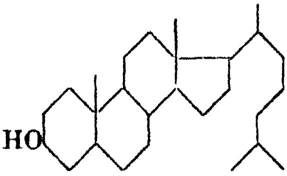
CHOLESTEROL



ERGOSTEROL



STIGMASTEROL



COPROSTEROL

THE BILE-ACIDS

Bile, a product of the liver, is stored in the gall bladder, and serves as an agent for promoting the absorption of fats and sterols by the intestinal tract.

It contains (in addition to inorganic salts and the bile-pigments) certain pseudopeptides which consists of the bile acids linked with amino-acid units, thus :—

$$C_{23}H_{36}(OH)_3CO\,.\,NH\,.\,CH_2COOH \xrightarrow{\qquad\qquad} C_{23}H_{36}(OH)_3COOH$$

Glycocholic acid — Cholic acid

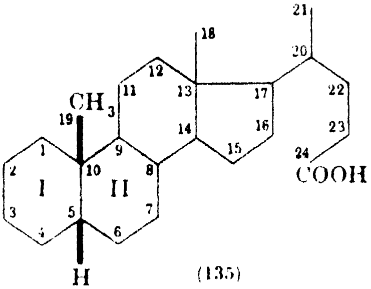
$$+\ NH_2CH_2COOH$$

Glycine

$$CH_{23}H_{36}(OH)_3\,.\,CO\,.\,NH\,.\,CH_2\,.\,CH_2SO_3H \nearrow +\ NH_2CH_2CH_2SO_3H$$

Taurocholic acid — Taurine

The hydrolysis of glycocholic and taurocholic acids yields cholic acid and the corresponding amino-acids. These bile acids are usually accompanied by the pseudo-peptides of other related acids, so that the hydrolysis of bile produces cholic acid accompanied by a number of related acids. The main examples are given in Table IV below, the structure of cholanic acid † (135) being taken as fixed ; it will be noted that the natural bile acids are hydroxy derivatives of cholanic acid or one of its stereo-isomers.



(135)

TABLE IV

Name of acid	Source	Position of —OH groups	Formula	Parent acids
Lithocholic	Man, ox	3t.*	$C_{24}H_{40}O_3$	Cholanic
Ursodesoxycholic	Bear	3t.,* 7c.	$C_{24}H_{40}O_4$	Ursocholanic
Hyodesoxycholic (α)	Pig and hippo	3t., 6	$C_{24}H_{40}O_4$	*allo*-Cholanic
Chenodesoxycholic	Man, ox, goose, duck	3t., 7t.	$C_{24}H_{40}O_4$	Cholanic
Desoxycholic	Man, ox, goat, sheep, deer	3t., 12	$C_{24}H_{40}O_4$	Cholanic
Nutriacholic	Beaver	Unknown	$C_{24}H_{40}O_5$	?
Phocæcholic (β)	Walrus, seal	3, 7, 23	$C_{24}H_{40}O_5$	?
Cholic	Man, ox, goat, sheep	3, 7, 12	$C_{24}H_{40}O_5$	Cholanic
Tetrahydroxy cholanic	Rabbit	3, 7, 8, 12	$C_{24}H_{40}O_6$	Cholanic

* t. = *trans*- ; c. = *cis*-.

It is neither useful nor expedient to attempt a summary of the enormous mass of data leading to the formulation of the bile acids, and attention is drawn to the following points :—

1. *Relation between the Sterols and Bile-acids*

Dehydration and hydrogenation of many of the bile-acids, cholic, desoxycholic, chenodesoxycholic and lithocholic acids leads to a saturated acid—cholanic acid, in each case. Cholanic acid (135) can also be obtained by the cautious oxidation of coprostane (136) with chromic acid, acetone being the other substance obtained in the reaction—

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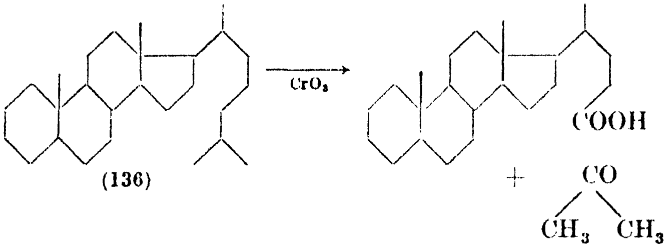
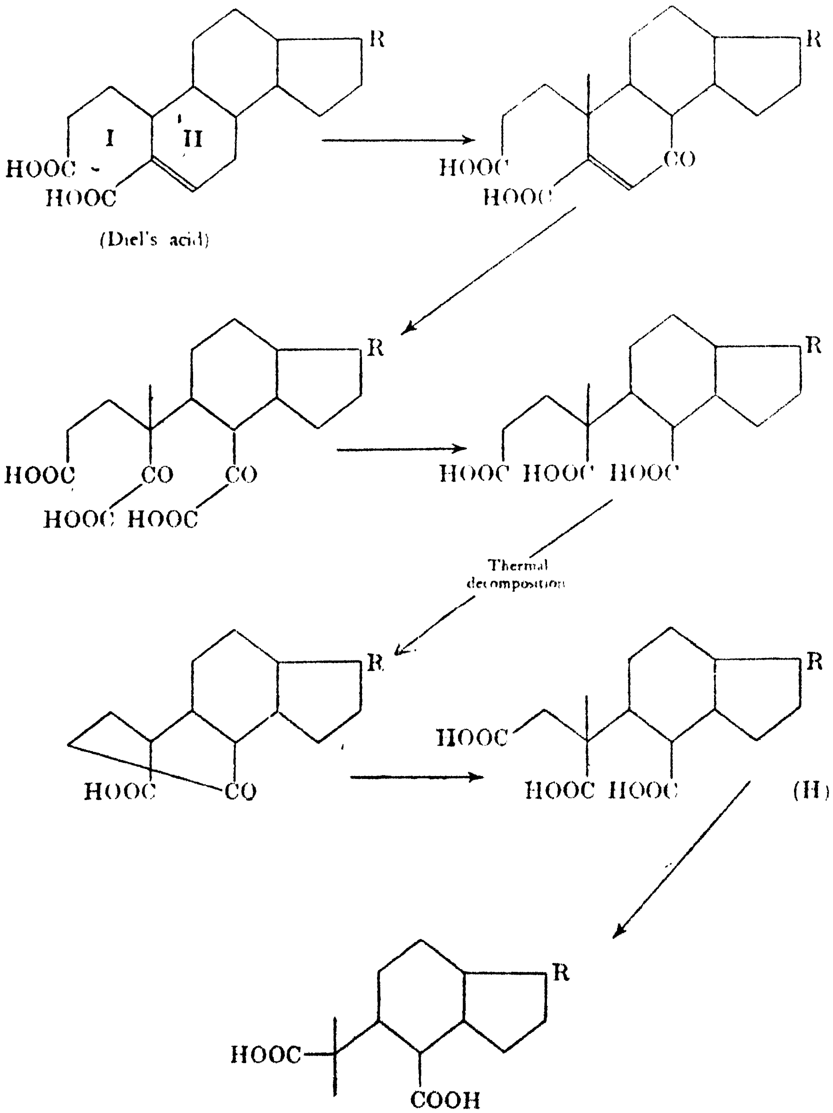
† Cholanic acid is the *cis*- form, as shown in (135) ; the corresponding *trans*- form is *allo*cholanic acid.



(136) (137)

Clearly, therefore, coprostane and cholanic acid are related simply through a variation in side-chain, and have a common ring structure.



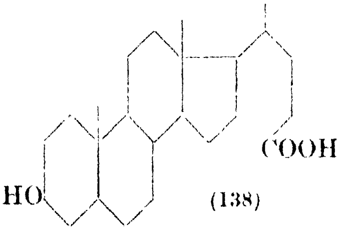
2. *The Central Nucleus*

Some indication of the methods by which the structure of the central nucleus of this series was established may be obtained from the following degradation of Diel's acid, obtained by the action of potassium hypobromite on cholesterol. Progressive oxidation gives the series of acids shown in the scheme below ; each stage has, of course, been carefully examined analytically and the conclusion may be drawn that since three carbon atoms are lost in the transformation to the acid (H), and since this acid can still yield a keto-acid on thermal decomposition, the original structure must have comprised two six-membered rings in the positions of I and II.

This is only a single example of many such degradations upon which rest the conclusions drawn concerning the main nucleus of the sterols. The modifications brought about by the presence of hydroxyl groups in the bile-acids in these degradations enable the positions of the hydroxyl groups to be fixed with a fair degree of certainty.

3. *The Hydroxyl Groups of the Bile-acids*

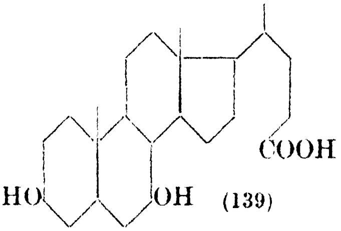
The position of the hydroxyl groups in the cholic acids was arrived at after careful consideration of the mass of evidence relating to the opening of the rings and the identification of the various degradation products ; the three principal members of the series are shown below :—



(138)

Lithocholic acid

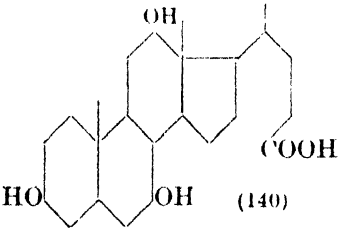
(3-Hydroxycholanic acid)



(139)

Chenodesoxycholic acid

(3 : 7-Dihydroxycholenic acid)



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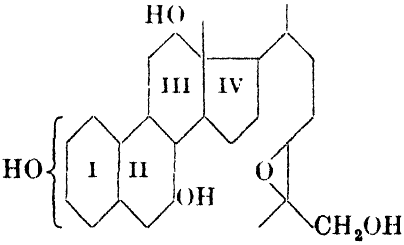
Cholic acid

(3, 7, 12-Trihydroxycholanic acid)



(141)

Substances of the bile acid group are by no means confined to the simple derivatives of the cholanic acids ; shark bile, for instance, contains the sulphuric acid ester of scymnol which is a neutral tetrahydric alcohol, probably having the structure (141), in which the position of the hydroxyl group in ring I is in doubt.

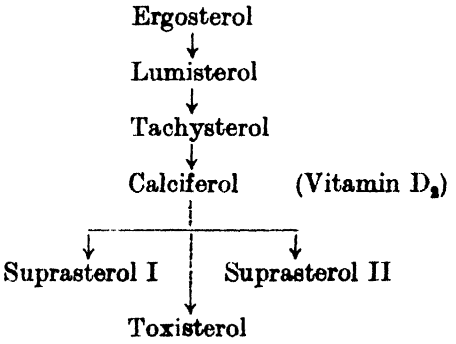
D VITAMINS

Since the structure and chemistry of the D vitamins is so closely related to that of the sterols, it is appropriate that they should be considered here rather than with the other vitamins to which they show little or no chemical relation.

It was recognised early in the history of vitamin study that various fish-liver oils and to a limited extent many other natural oils and fats contained, in their unsaponifiable fraction, an important accessory substance which exerts a profound effect on the proper formation of bone tissue ; in the absence of this factor, which was called vitamin D, bone fails to calcify properly and remains, especially at the terminals, soft and ill-adapted to carry the weight of a growing animal. This leads to a condition of deformity and malnutrition known as " rickets ", and from this term it became common to refer to the active principle of the curative vitamin D as the " antirachitic " vitamin. The function of vitamin D is, therefore, as a regulator of phosphorus-calcium metabolism.

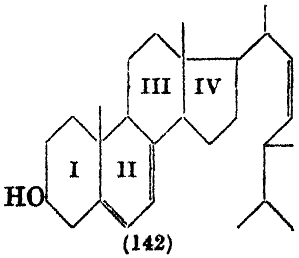
Before the structure of ergosterol was known with certainty, Steenbock and Hess observed that irradiation of solutions of ergosterol with ultra-violet light led to the formation of a substance of high antirachitic value which was thought to be identical with vitamin D. Although this substance has been shown to be a valuable antirachitic agent in therapy, and despite the fact that its active principle (calciferol) has been isolated in pure form, it is becoming increasingly evident that calciferol is not always identical chemically with the ' vitamin D ' from various natural sources, and that it is only one of a group of substances capable of exerting antirachitic action ; these are referred to as ' the D vitamins '. Calciferol is not, for example, identical with the D vitamin of fish-liver oils.

When ergosterol is subjected to ultra-violet irradiation a series of products is produced :—



The process is complete with the formation of the suprasterols which do not suffer further photochemical change, but there is evidence (both spectrographic and physiological) to show that another intermediate ' toxisterol ' is formed, mainly by over-irradiation ; however, the exact place of toxisterol in the above scheme is not certain.

Calciferol may also be de-activated by heat, pyrocalciferol and *iso*-pyrocalciferol being formed. Clearly all these changes must be considered relative to the structure of ergosterol (142)—



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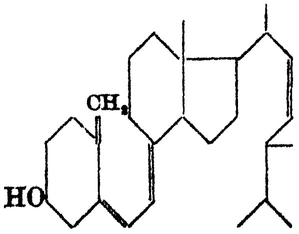
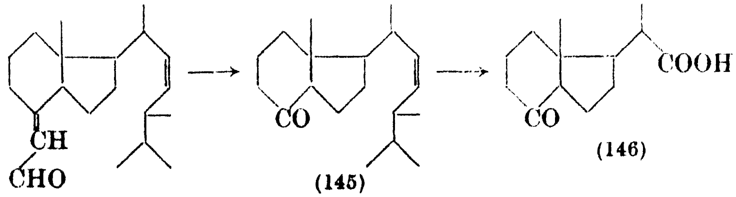


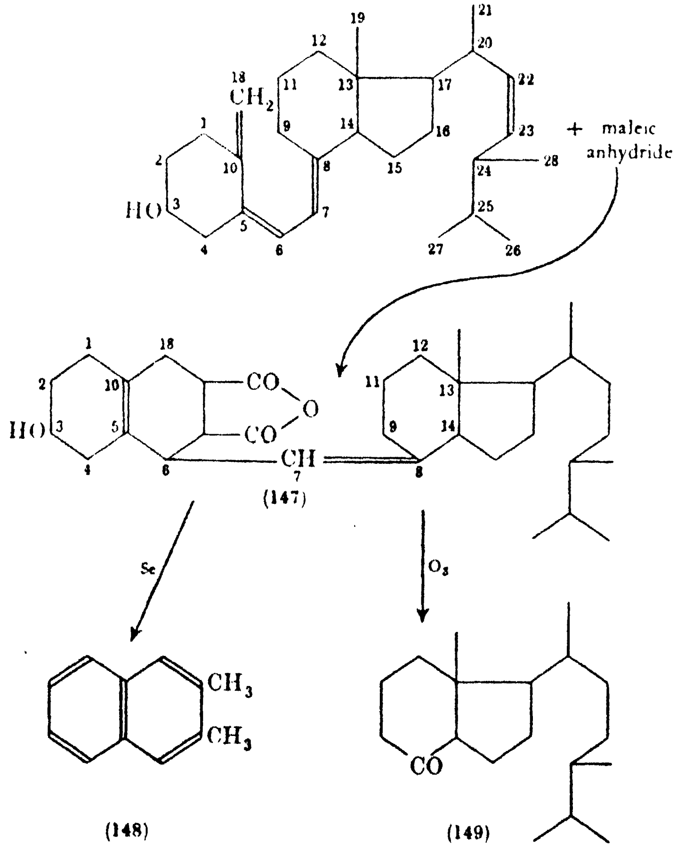
(143)

There is much evidence to show that calciferol is obtained by opening of ring II, giving a structure (143) which comprises an exocyclic methylene group ; Heilbron has shown that, by ozone oxidation and breakdown, calciferol may be converted progressively into the aldehyde (144), the ketone (145), and the ketonic acid (146). The formation of formaldehyde by ozone oxidation indicates an exocyclic methylene group,



(144) (145) (146)

Windaus and Thiele obtained from calciferol and maleic anhydride a Diels-Alder addition product (147) which they subjected to the action of selenium, when 2 : 3 dimethylnaphthalene (148) was obtained ; whilst on ozonic oxidation and hydrolysis, Heilbron's ketone (149) was obtained, indicating that maleic anhydride had added on across the conjugated system comprising the exocyclic methylene group and the 5 : 6 double bond, leaving the 7, 8 double bond intact :

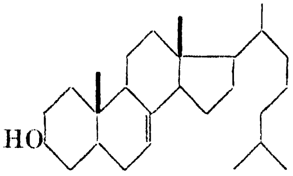


(147)

(148) (149)

The structure of calciferol (vitamin D_2) is, therefore, fixed with a fair degree of certainty. With regard to the other vitamins D, there appears to be at least five precursors (and more will almost certainly be discovered) which will give antirachitic substances on ultra-violet irradiation.

Between 1934 and 1938 it was shown that a number of other sterol derivatives gave antirachitic substances when subjected to ultra-violet irradiation. Thus Windaus and Langer[1] showed that 22-dihydro-ergosterol could be converted to an antirachitic vitamin (now known as vitamin D_4); Windaus, Lettré and Schenck[2] obtained a vitamin D_3 from the irradiation of 7-dehydrocholesterol (150), and various observations lead to the presumption that vitamin D_3 is identical with the natural D vitamin of fish-liver oils. A comparison of the properties of the three most prominent D vitamins is given in the Table V.



(150)

TABLE V

Name	M.P.	$[\alpha]_D$	Potency in International Units
Vitamin D_2 (Calciferol)	115–117°	+ 103° (ethanol)	40,000/mg.
Vitamin D_3	82–84°	+ 83·3° (acetone)	40,000/mg.
Vitamin D_4	107–108°	+ 89·3° (ethanol)	20–30,000/mg.

THE SEX HORMONES

Development and continuance of sexual functions in higher animals is dependent on the continued supply of sex hormones, many of which are cyclopentenophenanthrene compounds of obviously steroid origin. In the male, these hormones are synthesised in the testes; in the female, their origin is the ovary and corpus luteum. The process of their inception is complicated, and is controlled by the non-steroid hormones of the anterior lobe of the pituitary body. An the male, the hormones control the growth and function of the genital tract and organs and the longevity and motility of the sperm; in the female they are concerned with the more complex processes of the œstrus and pregnancy cycles.

THE ŒSTRUS HORMONES

In 1929 Doisy[3] and Butenandt[4] independently isolated a pure crystalline œstrogenic hormone from pregnancy urine. Since then, it has been obtained from a variety of sources, and is called 'œstrone'. Its empirical formula $C_{18}H_{22}O_2$, and general properties show it to be a derivative of a complex hydrocarbon, carrying one hydroxyl and one ketonic group. Together with œstrone

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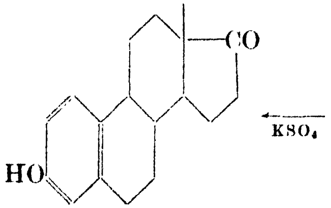
[1] Windaus and Langer, *Ann.*, 1933, **508**, 105.

[2] Windaus, Lettré and Schenck, *ibid.*, 1935, **520**, 98.

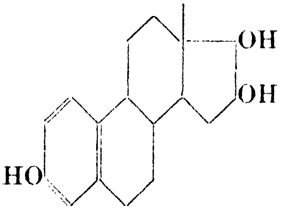
[3] Doisy, Veler and Thayer, *Am. J. Physiol.*, 1929, **90**, 329; *J. Biol. Chem.*, 1930, **86**, 499; **87**, 357.

[4] Butenandt, *Naturwissenschaften*, 1929, **17**, 879; B. and Zilgner, *Z. Physiol. Chem.*, 1930, **188**, 1.

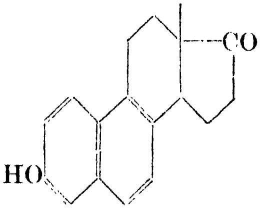
(151), there is frequently found a hydrate $C_{18}H_{22}O_2 . H_2O$, œstrol (152), which is related to œstrone thus :—



m.p. 255°
$[\alpha]_D = + 156 + 158°$
white crystals
(151)



white plates,
m.p. 280°
$[\alpha]_D = + 30°$
(152)



(153)

Although œstrone and its related compounds have been isolated from female sources, a far richer source is stallion urine. In addition to the substances already mentioned, mare's urine contains equilin, $C_{18}H_{20}O_2$, hippulin, $C_{18}H_{20}O_2$, and equilenin, $C_{18}H_{18}O_2$, the structure of which is (153).

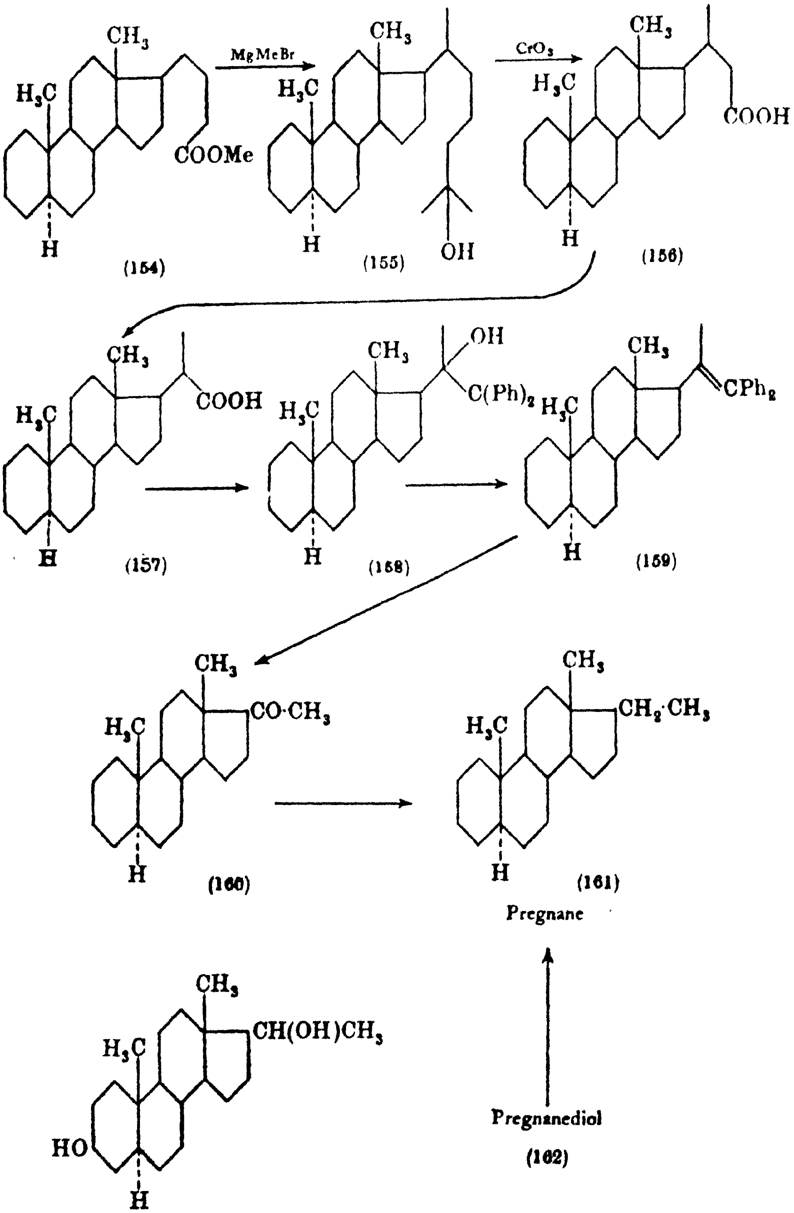
The structure of œstrone and its related compounds was not known with certainty until after Butenandt had elucidated the structure of pregnanediol, the follicular hormone isolated by Marrian in 1929. Pregnanediol (162) ($C_{21}H_{36}O_2$) has the properties of a di-secondary alcohol and on reduction with Clemmensen's reagent yields a hydrocarbon pregnane (161), the partial synthesis of which from *bis*norcholanic acid showed the nuclear structure of pregnanediol. When cholanic methyl ester (154) is treated with magnesium methyl bromide a dimethyl carbinol of the structure (155) can be obtained, and from it, by oxidation, the norcholanic acid (156) ; a similar process with phenyl magnesium bromide yields *bis*-norcholanic acid (157) by loss of a further methylene group from the 17-side-chain. The formation of the diphenyl carbinol (158) is carried out by two successive treatments of *bis*-norcholanic ester with phenylmagnesium bromide. On dehydration, it yields the unsaturated hydrocarbon (159) which, on ozonisation and hydrolysis, gives benzophenone and a ketone (160) known as œtiocholyl methyl ketone, and this, on reduction with Clemmensen's reagent is converted to pregnane (161), identical with that obtained from pregnanediol (162). In this way, the linkage between pregnanediol and the steroid group is made clear, but the location of the two hydroxyl groups is not elucidated by the chain of reactions just described.

The location of the two secondary alcoholic groups depends on the formation by oxidation of pregnanedione (164) which can be demonstrated to be a 17-aceto compound, and which, on further oxidation by opening ring I in the 3–4 position gives a keto-dicarboxylic acid (165). Since this behaviour is shown by so many other compounds of the steroid group carrying a hydroxyl group at " 3 ", it is assumed that pregnanediol is a 3, 20 diol (163).

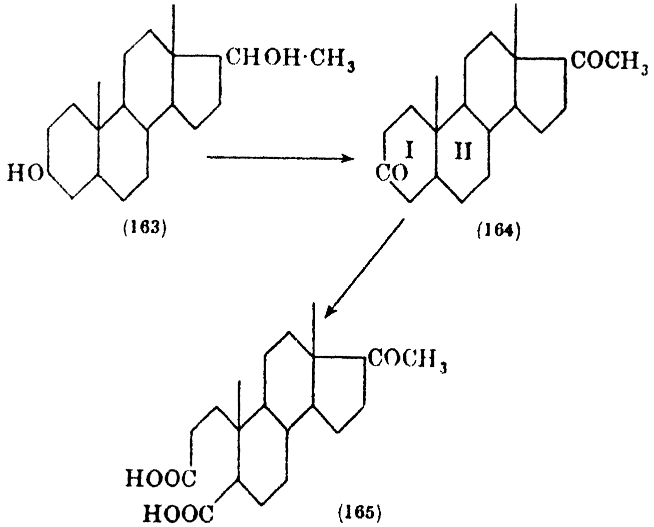
Although the structure of pregnanediol was thus made clear, no light was thrown on that of œstrone which was, at that time, thought (on X-ray arguments, since proved unsound) to be entirely dissimilar.

In 1932 and 1933, however, evidence for a steroid structure had begun to accumulate and œstriol (167) was oxidised by caustic fusion to a dicarboxylic acid (168) which, on selenium dehydrogenation, gave a 1, 2 dimethylphenanthrol (169). The structure of this phenanthrol was elucidated by distillation with zinc-dust when 1, 2 dimethylphenanthrene was obtained. Both the latter hydrocarbon and the methyl ether of its 7-hydroxy derivative (170) have been synthesised and shown to be identical with the compounds from natural œstriol.

The synthesis of 1, 2-dimethylphenanthrene has already been discussed, (Chap. III, p. 172); that of 7-methoxy-1, 2-dimethylphenanthrene is outlined



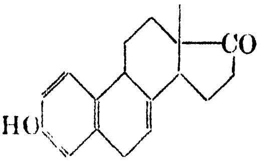
below: β-Naphthyl-methyl ether (175) is condensed with propionyl chloride in nitrobenzene (Friedel-Crafts reaction; aluminium chloride catalyst), giving 2-propionyl-7-methoxy naphthalene (176); side-chain bromination (174), followed by a malonic ester condensation, yields the acid (173) which now carries a nuclear bromine atom; this, however, is incidental, and is removed at a later stage. The second methyl group is introduced by a Grignard reaction followed by dehydration of the tertiary alcohol yielding the unsaturated acid (171), which, under the influence of palladium and hydrogen not only loses its double bond by reduction to a saturated chain, but also loses the nuclear bromine atom (172). Cyclisation with stannic chloride, and selenium dehydrogenation then yields 7-methoxy-1, 2-dimethylphenanthrene (170).



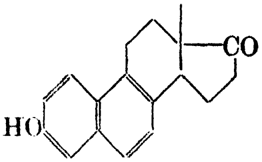
(163) (164) (165)

Further evidence clinching the structure of œstrone was obtained by reducing œstrone methyl ether (177) to the compound (178), dehydrogenating with selenium to 7-methoxycyclopentenophenanthrene (179), a substance which was synthesised by Cook and his co-workers by the method outlined on page **917**.

There seems little doubt, therefore, that this structural conception of œstrone and œstriol is essentially accurate. Equilin and equilenin are formulated :—



Equilin (m.p. 240°)



Equilenin (m.p. 258°)

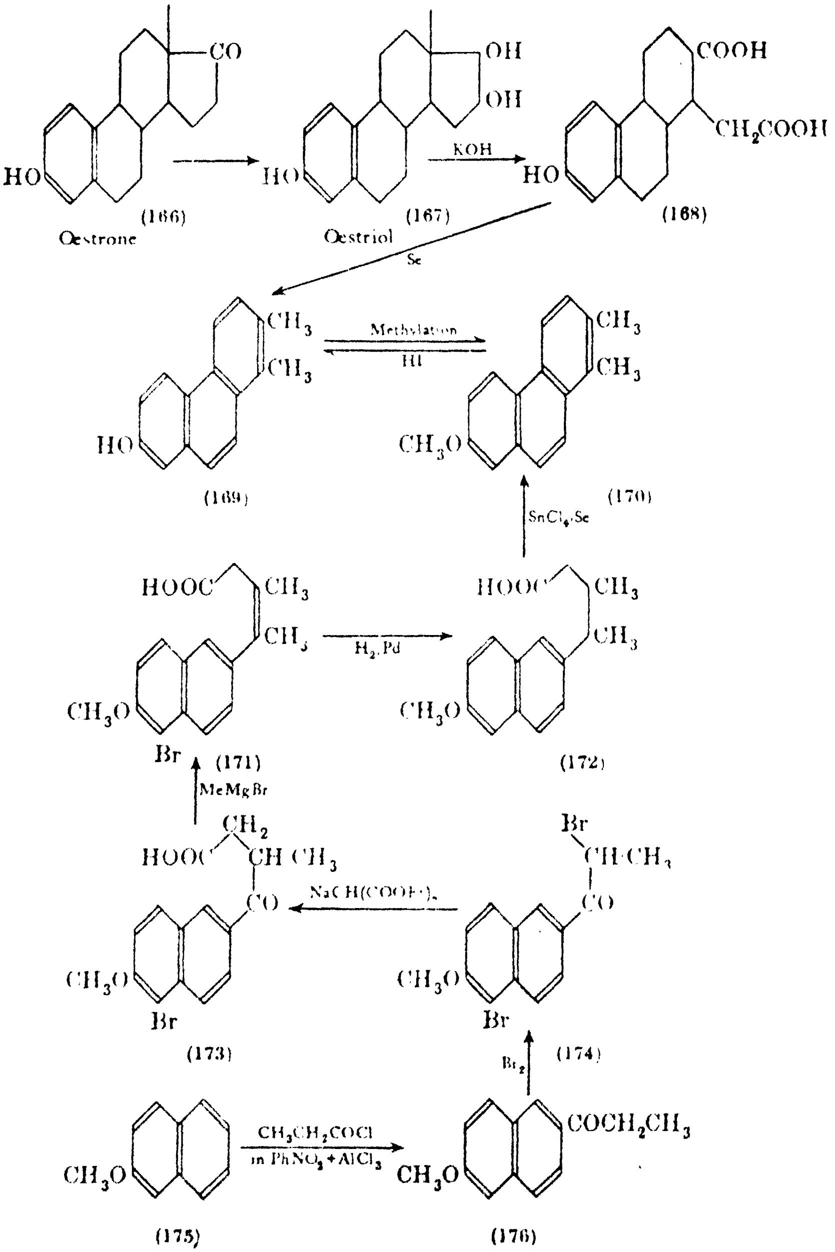
PROGESTERONE

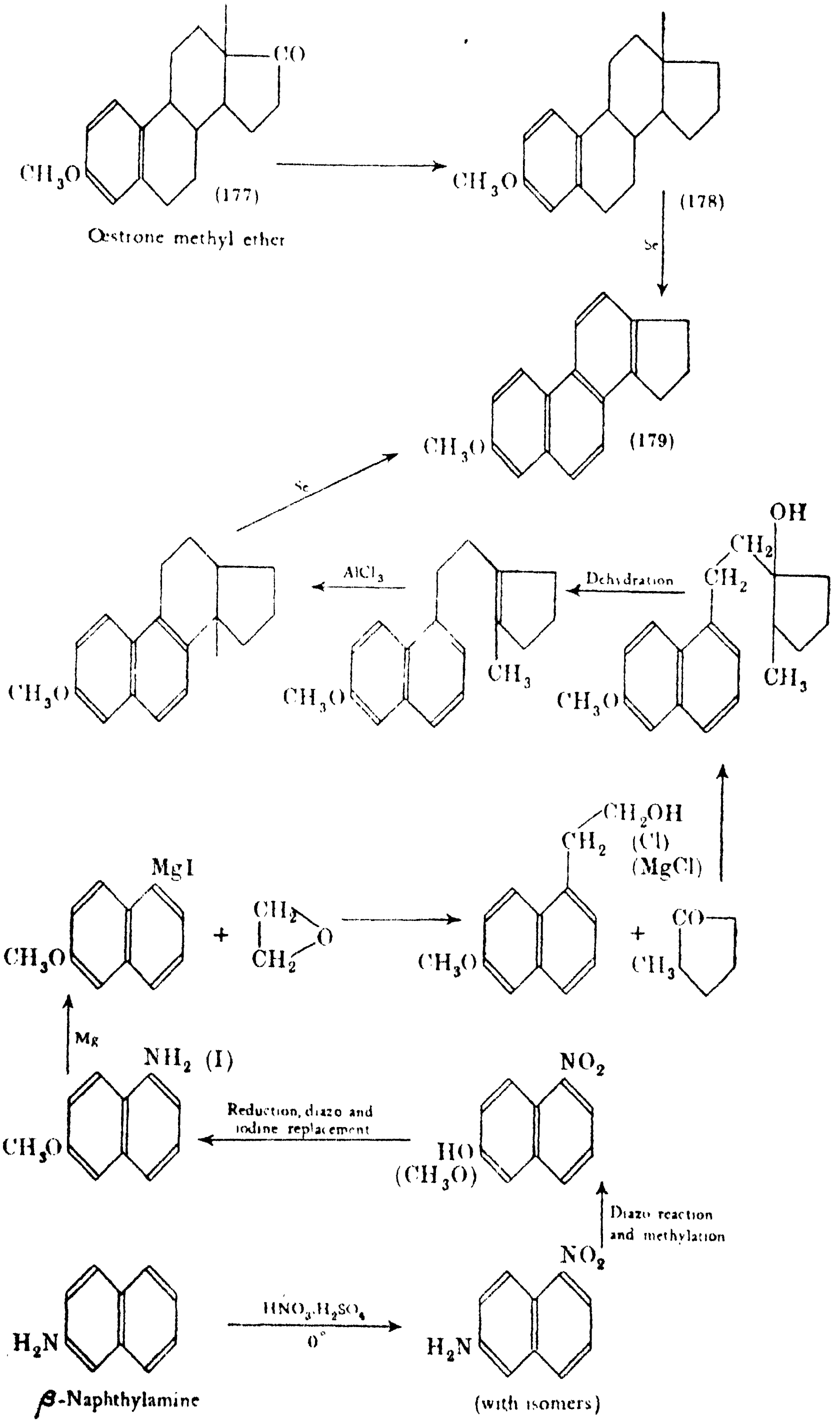
The corpus luteum, or yellow body, is a tissue of the ovary concerned with the preparation for and maintenance of pregnancy. The methods by which this control is attained and carried out are beyond the scope of this work except insofar as the hormone progesterone is concerned. Progesterone was obtained as a pure crystalline active principle (m.p. 128° : $[\alpha]_D = +192°$) in 1933–1934 by Butenandt [1] and others,[2] together with another closely related diketone and an inactive hydroxyketone. The relation of the compounds to pregnanediol (181) was shown by the conversion of both the inactive hydroxyketone and

---

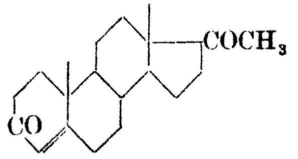
[1] Butenandt, *Wien. Klin. Woch.*, 1934, **80**, 934.

[2] Slotta, Ruschig and Fels, *Ber.*, 1934, **67**, 1270; Allen and Wintersteiner, *Science*, 1934, **80**, 190.

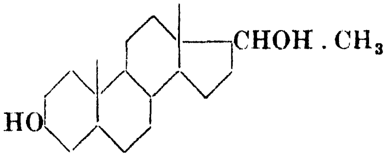

HO
CO
(166)
Oestrone
HO
OH
OH
(167)
Oestriol
KOH
HO
COOH
CH₂COOH
(168)
Se
HO
CH₃
CH₃
(169)
Methylation
HI
CH₃O
CH₃
CH₃
(170)
SnCl₄, Se
HOOC
CH₃
CH₃
CH₃O
Br
(171)
H₂, Pd
HOOC
CH₃
CH₃
CH₃O
(172)
MeMgBr
CH₂
HOOC
CH CH₃
CO
CH₃O
Br
(173)
NaCH(COOEt)₂
Br
CH·CH₃
CO
CH₃O
Br
(174)
Br₂
CH₃O
(175)
CH₃CH₂COCl
in PhNO₂+AlCl₃
CH₃O
COCH₂CH₃
(176)


CO
CH₃O
(177)
Oestrone methyl ether
CH₃O
(178)
Se
CH₃O
(179)
Se
AlCl₃
Dehydration
OH
CH₂
CH₂
CH₃
CH₃O
CH₃
CH₃O
CH₃O
CH₂OH
CH₂ (Cl)
(MgCl)
MgI
CH₃O
CH₂
O
CH₂
CH₃O
CO
CH₃
Mg
NH₂ (I)
CH₃O
Reduction, diazo and iodine replacement
NO₂
HO
(CH₃O)
Diazo reaction and methylation
NO₂
H₂N
HNO₃.H₂SO₄
0°
H₂N
β-Naphthylamine
(with isomers)

pregnanediol into the same saturated diketone upon oxidation. This led to the suggested formula for progesterone (180)—

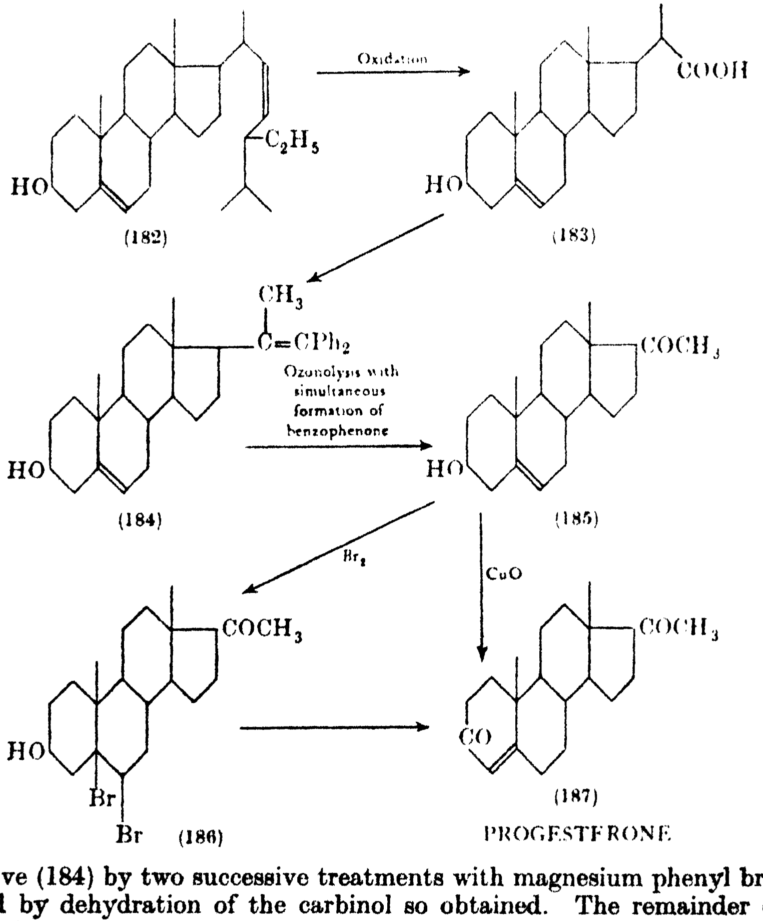


Progesterone
(180)



Pregnanediol
(181)

which is confirmed by the partial synthesis from stigmasterol[1] (182). This sterol was converted by methods similar to those already described (oxidation) to 3-hydroxybisnorcholanic acid (183), the ester of which yielded diphenyl



derivative (184) by two successive treatments with magnesium phenyl bromide followed by dehydration of the carbinol so obtained. The remainder of the steps leading to progesterone are shown in the formulæ (185) to (187), and are similar to those previously described (p. 915).

SYNTHETIC ŒSTRUS AND CARCINOGENIC COMPOUNDS

Demonstration that the sex hormones and steroids were related led to a detailed consideration of their physiological relation to synthetic hydrocarbons and to the known carcinogenic compounds. In the first place, the œstrus effect is produced by a large number of apparently unrelated compounds. Thus Cook and Dodds[1] obtained a series of 1, 2, 5, 6-dibenzanthraquinone derivatives (188) by the action of the Grignard reagent on the parent body.

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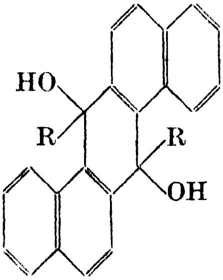
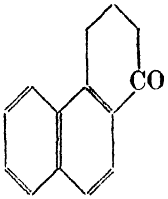
[1] Butenandt, *Ber.*, 1934, **67**, 1901 and 2085; Fernholz, *Ber.*, 1934, **67**, 1855 and 2027.



(188)



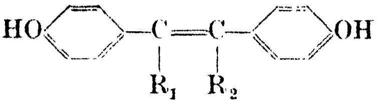
(189)

Many of the compounds are œstrogenic, but a curious variation exists between the activities of the members of the series as shown in Table VI below :—

TABLE VI

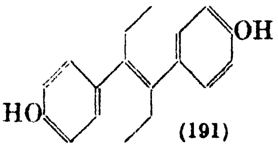
Group R of formula (188)	Œstrogenic dose (for mice)
Methyl	Inactive in 100 mg. dose
Ethyl	1·0 mg.
n-Propyl	0·025 mg.
n-Amyl	Inactive

Similarly, 1-ketotetrahydrophenanthrene (189) is œstrogenically active. Exceptional œstrogenic activity has been discovered in certain derivatives of stilbene by Dodds and his co-workers. This intense activity is associated with the 4, 4′-dihydroxyl-α, β-dialkyl stilbenes (190)—



$HO\cdot C_6H_4\cdot C(R_1){=}C(R_2)\cdot C_6H_4\cdot OH$

(190)



(191)

Table VII below shows the variation in activity with nature of the group R_1 and R_2 ; it will be observed that the activity of the methylethyl, and diethy derivatives exceeds that of œstrone itself (700,000 units).

TABLE VII

SHOWING OESTROGENIC ACTIVITIES OF 4, 4′-DIHYDROXY-α, β-DIALKYL STILBENE DERIVATIVES

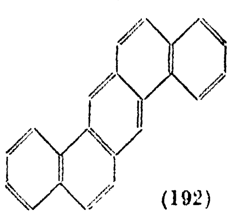
Groups		Activity in œstrogenic units per gm.
R_1	R_2	
H	H	140
H	Et	5,000
Me	Me	40,000
Me	Et	1,000,000
Et	Et	3,000,000
n-C_3H_7	*n*-C_3H_7	300,000
i-Pr	*i*-Pr	50,000
Bu	Bu	5,000

---

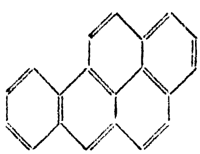
[1] Cook and Dodds *et al.*, *Proc. Roy. Soc.*, 1934, **114B**, 272.

It is, perhaps, instructive to rewrite the formula of the most active compound as in (191) by which its remarkable resemblance to the sterols is made apparent. The apparently large number of compounds which show œstrogenic activity prompted Kögl to remark, even as early as 1933 at the British Association meetings at Leicester, that "in the case of the follicular hormone (œstrone) it has been found that the 'lock' can be opened not only by the classical 'key', but also more or less easily by rough copies, or even skeleton keys".

There is some evidence to show that certain types of cancer are due to over-production or inadequate utilisation of œstrogens. Although they are not primarily of steroid structure, this appears to be an appropriate point for some mention of the *carcinogenic hydrocarbons*. In cancer, cells that would normally multiply in a simple orderly fashion under control of a limiting factor, appear to multiply continually without control and to form large masses of undesired cell tissue, or tumours. The recognition that this condition can develop as an occupational disease (as in tar-cancer) has led to examination of many hydrocarbons, and to the discovery that many of them are specific carcinogenic agents. Thus, 1, 2, 5, 6-dibenzanthracene (192) has been shown to be capable of initiating cancer whilst Cook[1] and his co-workers have also been able to show that the activity carcinogenic 1 : 2-benzpyrene (193) is an actual constituent of coal-tar pitch. From two tons of pitch, a small quantity of 1 : 2-benzpyrene was isolated indicating that the material itself contained about 0·003 per cent.

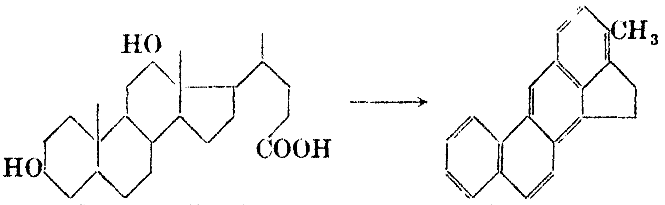


(192)



(193)

It is at this stage that a definite link was established between the causation of cancer and the chemistry of the steroids. Whilst the isolation of carcinogenic hydrocarbons and their laboratory synthesis gave an adequate rationale for occupational cancer, it appeared to have little to do with the ordinary forms of cancer produced in a non-occupational manner. When, however, Wieland[2] was able to degrade desoxycholic acid by four simple steps to methyl-cholanthrene—



Desoxycholic acid Methylcholanthrene

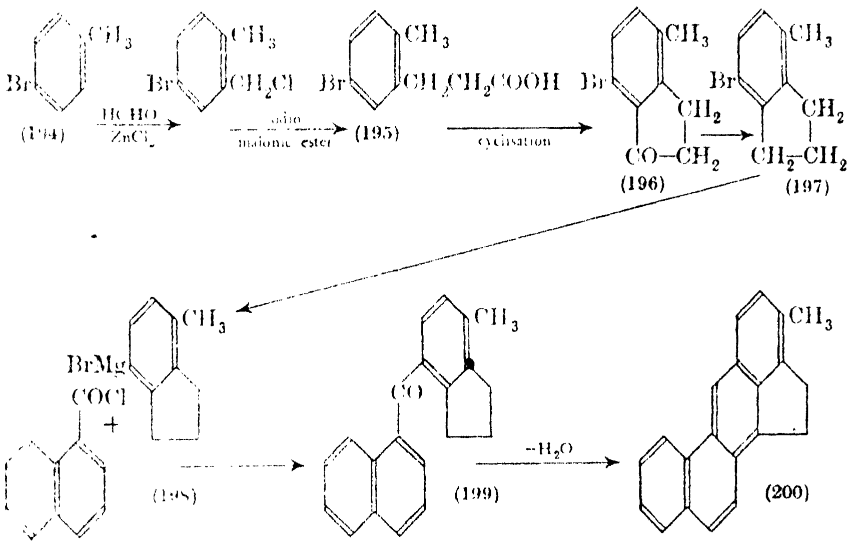
and when it was demonstrated by Cook that methylcholanthrene is powerfully carcinogenic, a different complexion was put upon the matter. Although definite proof is lacking that cholic acid or steroid substances are converted in the body by some aberration into carcinogenic hydrocarbons, it is a probability which must be included in all future investigations on this subject.

The synthesis of methyl cholanthrene (200) has been achieved in a variety of ways; Fieser and Seligman[1] used a method which starts from nuclear substituted hydrindenes. Thus, when formaldehyde, hydrogen chloride and zinc chloride are allowed to react on *p*-bromotoluene (194) a mixture of chlormethyl-*p*-bromotoluenes is obtained, which when reacted with malonic ester yields the corresponding substituted acetic acid (195); cyclisation gives the corresponding hydrindone (196), and reduction of the latter gives the hydrindene (197)—4-methyl-7-bromohydrindene. The two original chlormethyl derivatives give the same hydrindene, so that separation is unnecessary. When the hydrindene is converted to its Grignard compound, this reacts with α-naphthoyl chloride (198) to give the ketone (199). This, on heating, gives an intramolecular loss of water (Elbs reaction) with formation of a 45 per cent. yield of methylcholanthrene (200).

---

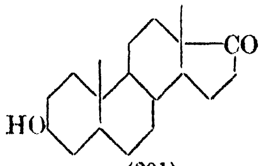
[1] Cook *et al., J.C.S.*, 1930, 1087; 1931, 487, 489, 499, 2012, 2524, 2529, 3273; 1932, 456, 1472; 1933, 395, 1408, 1592.

[2] Wieland and Schlichting, *Z. Physiol. Chem.*, 1925, **150**, 267. Wieland and Dane, *Z. Physiol. Chem.*, 1933, **219**, 240.



Male Sex Hormones

In 1931 Butenandt and Tscherning[2] first isolated the male sex hormone androsterone, in crystalline form. His raw material was 15,000 litres of urine from which only 15 mg. of hormone was obtained; subsequent improvements in the methods of assay and extraction showed that male urine contains about 100 mg. of hormone per 100 litres, of which about one-quarter is capable of extraction in the pure form (m.p. 182–183°). The formula of androsterone ($C_{19}H_{30}O_2$) points to a steroid structure and Butenandt suggested (201)—



(201)

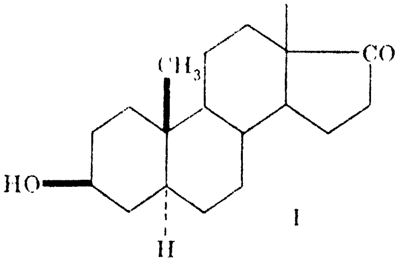
as the structure. Ruzicka[3] pointed out that such a structure should be obtained by oxidation of sterols containing a saturated ring system; by oxidation of the acetate of dihydrocholesterol he obtained a small quantity of ketonic material, which, when hydrolysed, gave a substance similar to androsterone in physiological action, but was clearly, from physical data, not identical

---

[1] Fieser and Seligman, *J.A.C.S.*, 1935, **57**, 228, 942.

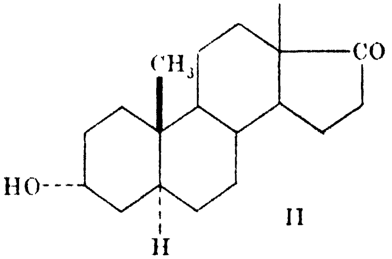
[2] Butenandt and Tscherning, *Nature*, 1932, **130**, 238; see also *Z. angew. Chem.*, 1931, **44**, 905.

[3] Ruzicka, Goldberg and Brügger, *Helv. Chim. Acta*, 1934, **17**, 1389.



I

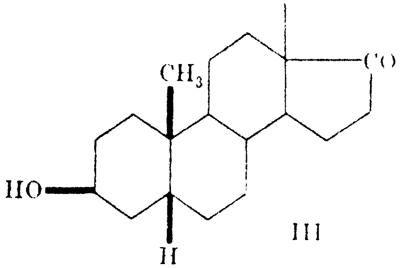
From dihydrocholesterol



II

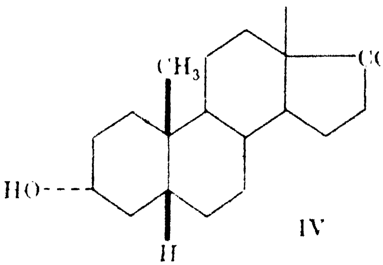
ANDROSTERONE

From *epi*dihydrocholesterol



III

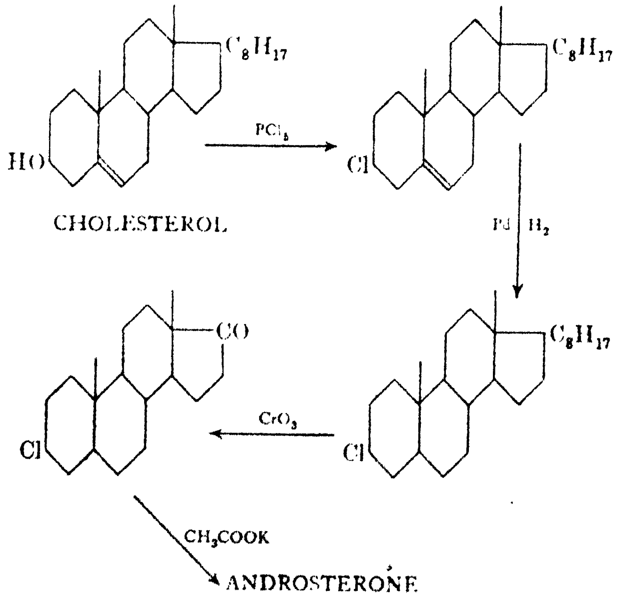
From coprosterol



IV

From *epi*coprosterol

with androsterone. Ruzicka concluded that it was a geometrical isomer, and continued his researches by preparing the four geometrically isomeric substances, the second of which was identical with natural androsterone. The latter may also be obtained by Marker's[1] process from cholesterol, thus—



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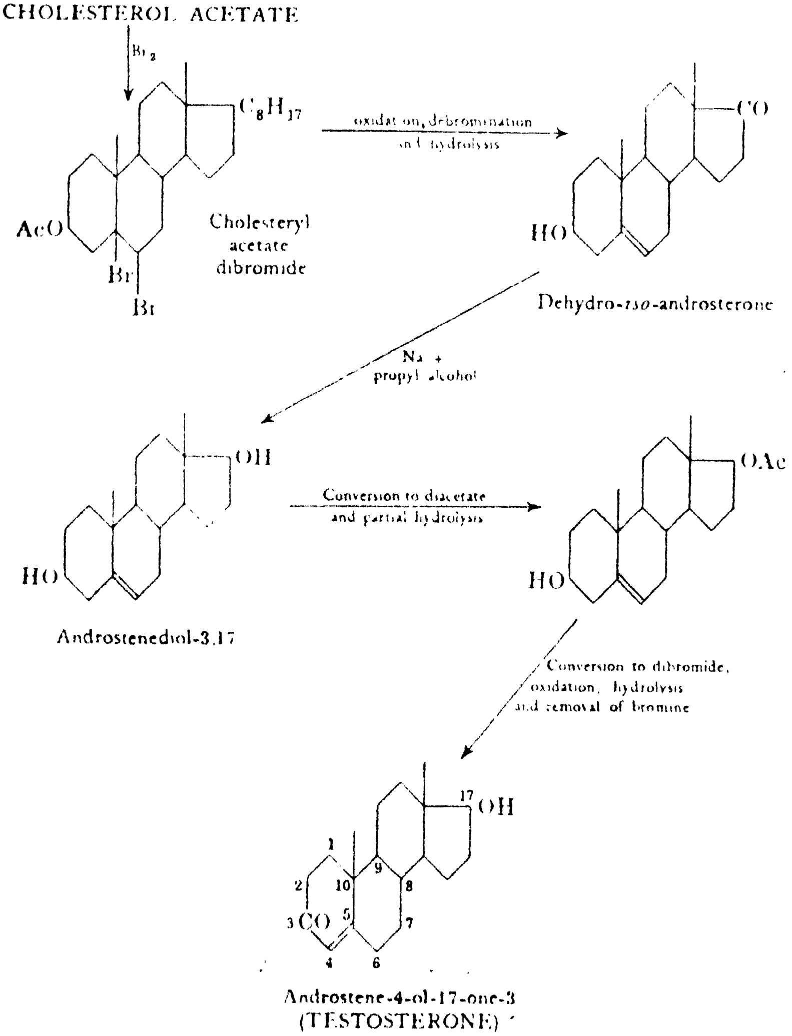
[1] Marker, *J.A.C.S.*, 1935, 57, 1755, 2358.

At one stage in this process, a Walden inversion must take place, but the precise point of such a change is not clear.

In 1935 Laqueur and David[1] isolated a hormone testosterone from testes; another male hormone of the same class is androstenediol-3, 17; testosterone (androstene-4-ol-17-one-3) can be obtained by the following sequence of reactions—


CHOLESTEROL ACETATE
Br₂
C₈H₁₇
AcO
Br
Br
Cholesteryl acetate dibromide
oxidation, debromination and hydrolysis
CO
HO
Dehydro-iso-androsterone
Na + propyl alcohol
OH
HO
Androstenediol-3,17
Conversion to diacetate and partial hydrolysis
OAc
HO
Conversion to dibromide, oxidation, hydrolysis and removal of bromine
17 OH
1
2
3 CO
4
5
6
7
8
9
10
Androstene-4-ol-17-one-3
(TESTOSTERONE)

Hormones of the Adrenal Cortex

The nature and activity of the hormones of the adrenal cortex has proved one of the most intricate and difficult problems, both from the chemical and biochemical viewpoints that has yet been brought under review. It is clear that the specialised function of the adrenal cortex (as distinct from the adrenalin-secreting portion of the gland) is the elaboration and secretion of a group of

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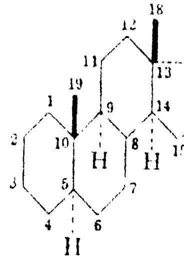
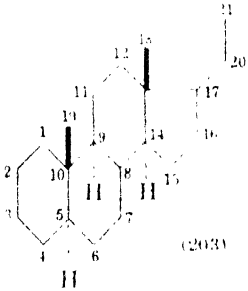
[1] Laqueur and David, *Z. Physiol. Chem.*, 1935, **233**, 281.

hormones which are life-maintaining in the sense that life cannot be maintained for more than a few hours after their complete deprivation. In the adrenalectomised animal, life can be prolonged by the injection of an adrenocortical extract. Chemical examination of adrenocortical extracts showed them to contain crystalline and amorphous substances, the former of which showed considerable activity, which is, however, surpassed by the action of the amorphous substances.[1]

Nothing is yet known of the chemical nature of the amorphous fraction, but the crystalline portion was found to be surprisingly complex, containing approximately thirty steroids most of which are derived from androstane (202), and its 17-ethyl compound, *allo*pregnane (203).



(202)



(203)

The chief modifications met with in the development of these derivatives are :—

(1) The -4, 5- double bond, making many of the compounds derivatives of androstene-4, or of pregnene-4.
(2) The presence of a hydroxy group at '21'.
(3) The presence of a hydroxyl- or keto- group at any or all of the positions —3, 11, 17, 20.

For convenience a hydroxyl marked 'α' will be considered to be below the plane of the ring; one marked 'β' above that plane; in formulæ, as previously, this is indicated by dotted (α) and heavy (β) links.

The commonest examples shown in Table VIII indicate that the pregnane derivatives always carry an oxygen-holding group at positions 3 and 20. In addition to the substances set out in the table, a few steroids of unknown composition have been isolated forming an intermediate class between the crystalline and amorphous fractions. There are, of course, other non-steroid components of the adrenocortical extract, proteins and simple peptides having been isolated, e.g., leucylproline, together with sulphoxides and sulphones, e.g., ββ-dihydroxydiethyl sulphoxide and dimethyl sulphone. It may be added that not all the steroid substances are equally active physiologically. The most active (after the amorphous fraction) is desoxycorticosferone acetate (pregnene-4, ol-21, dione-3, 20, acetate). It is of interest to note in passing that Linnell and Ronshdi[2] have prepared a number of synthetic substances which exhibit the activity of desoxycorticosterone acetate, but without the same intensity. The most successful which has one-hundredth of the action of

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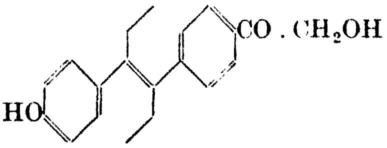
[1] Pfiffner, Wintersteiner and Vars, *J. Biol. Chem.*, 1935, **111**, 585. Wintersteiner and Pfiffner, *ibid.*, 1936, **116**, 291.

[2] Linnell and Ronshdi, *Nature*, 1941, **148**, 595.

TABLE VIII

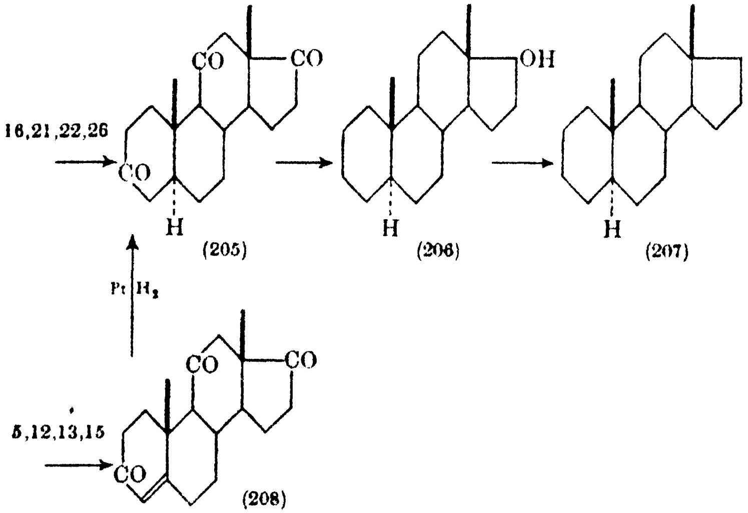
Empirical formula	4, 5-unsaturated link	Substituents in positions					Shortened name	Physical properties		
		3	11	17	20	21		M.P.	t°	$[\alpha]^{D}_{t^\circ}$
							ANDROSTANE SECTION			
1. $C_{19}H_{24}O_3$	+	CO	CO	CO			Andrenosterone	223–224°	20°	+ 262° ± 5° ethanol
2. $C_{19}H_{26}O_2$	+	CO	—	CO				—	—	—
3. $C_{19}H_{30}O_3$	—	OH(β)	OH(β)	CO				234–235°	20°	+ 84·5° ± 3° ethanol
							allo-PREGNANE SECTION			
4. $C_{21}H_{28}O_4$	+	CO	CO		CO	OH	11-Dehydrocorticosterone	177–180°	25°	α5461 = + 299° ± 1°
5. $C_{21}H_{29}O_5$	+	CO	CO	OH(β)	CO	OH	17-Hydroxydehydrocorticosterone	215°	25°	+ 209° ± 1° ethanol
6. $C_{21}H_{30}O_2$	+	CO	—	—	CO	—	Progesterone	α, 121° β, 128°	15°	+ 192°
7. $C_{21}H_{30}O_3$	+	CO	—	—	CO	OH	11-Desoxycorticosterone			
8. $C_{21}H_{30}O_3$	+	CO	—	OH(β)	CO	—	17-Hydroxyprogesterone	222–223°	17°	+ 105·6° ± 2° chloroform
9. $C_{21}H_{30}O_4$	+	CO	CO	—	OH	OH				
10. $C_{21}H_{30}O_4$	+	CO	—	OH(β)	CO	OH		213°	—	—
11. $C_{21}H_{30}O_4$	+	CO	OH	—	CO	OH	Corticosterone	180–182°	15°	+ 223° ± 3° ethanol
12. $C_{21}H_{30}O_5$	+	CO	OH(β)	OH(β)	CO	OH	17-Hydroxycorticosterone	207–210°	22°	+ 167° ± 2° ethanol
13. $C_{21}H_{30}O_5$	+	CO	CO	OH(β)	OH	OH		208°	—	—
14. $C_{21}H_{32}O_4$	—	OH(β)	CO	—	CO	OH		189–191°	19°	+ 93·8° ± 2° ethanol
15. $C_{21}H_{32}O_5$	+	CO	OH(β)	OH(β)	OH	OH	(Monohydrate)	125°		+ 87° ± 2° ethanol
16. $C_{21}H_{32}O_5$	—	OH(β)	CO	OH(β)	CO	OH		238–242°	16°	+ 61·8° ± 2° dioxane
17. $C_{21}H_{34}O_2$	—	OH(β)	—	—	CO	—		—	—	—
18. $C_{21}H_{34}O_3$	—	OH(β)	—	OH(β)	CO	—		—	—	—
19. $C_{21}H_{34}O_4$	—	OH(β)	OH	—	CO	OH		202–204°	—	—
20. $C_{21}H_{34}O_4$	—	OH(β)	—	OH(β)	CO	OH		—	—	—
21. $C_{21}H_{34}O_5$	—	OH(α)	OH	OH(β)	CO	OH		273–276°	15°	+ 73° ± 4° ethanol
22. $C_{21}H_{34}O_5$	—	OH(β)	OH(β)	OH(β)	CO	OH		220–225°	13°	+ 50·7° ± 3° dioxane
23. $C_{21}C_{36}O_3$	—	OH(β)		OH(β)	OH(α)	—		222–223°	20°	— 12·6° ± 2° methanol
24. $C_{21}H_{36}O_3$	—	OH(β)	—	OH(β)	OH(β)	—		216–217°	19°	— 7·9° ± 1° ethanol
25. $C_{21}H_{36}O_4$	—	OH(β)	—	OH(β)	OH(β)	OH(β)		198–200°	21°	— 1° ± 2° ethanol
26. $C_{21}H_{36}O_5$	—	OH(β)	OH(β)	OH(β)	OH(β)	OH		221–222°	19°	— 16° ± 1° ethanol

desoxycorticosterone acetate is reminiscent of stilbœstrol, and is 3, 4-diphenylhexene-3 (204), with a *para*hydroxyl group in one phenyl and a *para* —CO . CH_2OH group in the other.



(204)

The determination of the structure of all the substances mentioned in the table above is outside the scope of this book, but reference should be made to the excellent summary of work done up to 1941, by Reichstein and Shoppee.[1] Briefly, the main methods of establishing the nuclear structures are as follows. Substances 16, 21, 22 and 26 (Table VIII) all yield the same triketone (205) on chromic oxidation, and substances 5, 12, 13 and 15 all yield the closely related unsaturated triketone (208) which may be converted into the saturated *allo*-pregnane triketone (205) by reduction with hydrogen and platinum. Clemmensen's reagent reduces the saturated triketone to androstane (207) through the alcohol androstanol-17*b* (206).



This is an indication of the nuclear carbon skeleton of the eight substances, but does not give clues as to the position of the oxygenated groups; for the elucidation of the latter in various combinations of the 3, 11, 17, 20 and 21 positions, the reader is referred to Reichstein and Shoppee (*loc. cit.*).

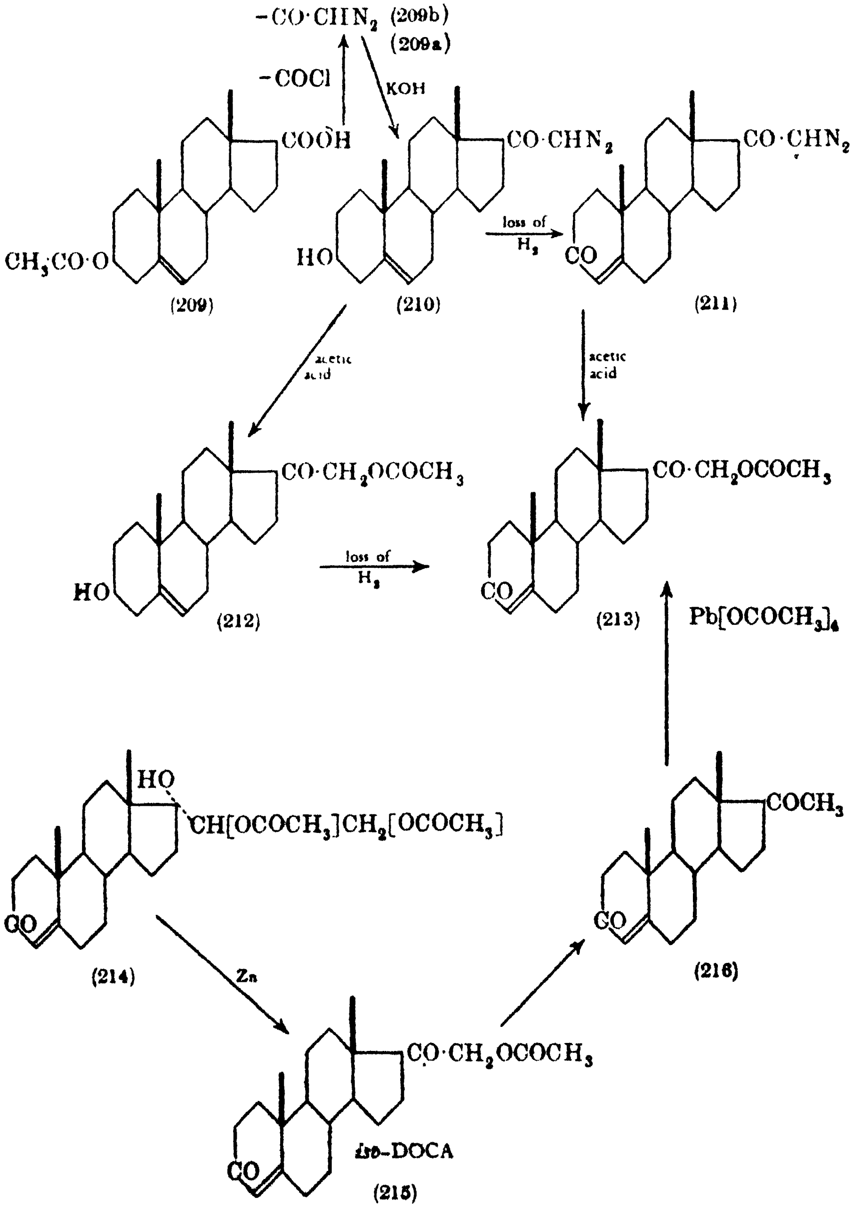
Not all the substances isolated from the adrenocortical extract are strongly active physiologically; apart from the amorphous portion, the most strongly active substance of the group is desoxycorticosterone (the activity of which is enhanced in its acetate—referred to for convenience as 'Doca'). Several methods have been successfully applied for the partial synthesis of desoxycorticosterone.

(1) Ehrhart *et al.*[2] showed that desoxycorticosterone acetate (213) was obtained by the direct oxidation of progesterone (216) in acetic acid solution with lead tetra-acetate. The yield is extremely poor.

[1] Reichstein and Shoppee, " Vitamins and Hormones ", p. 345, 1943, N. York.
[2] Ehrhart, *et al.*, *Münch. Med. Woch.*, 1939, **86**, 444.

(2) The keto-triol diacetate (214) has been converted to the *iso*-desoxycorticosterone acetate (17-*iso*DOCA) (215) by the action of zinc. The isomerism between this compound and DOCA is at carbon ' 17 ', and is geometrical in nature.

(3) Perhaps the best partial synthesis of desoxycorticosterone is from 3 β-acetoxyœtiocholen-5-acid-17 (209) the acid chloride of which (209*a*) is converted by diazomethane to the acetoxydiazoketone (209*b*) ; this, in turn, is converted to the free hydroxyl compound by caustic potash (210) and to the acetate (212) by boiling with acetic acid. After protection of the unsaturated group oxidation with chromic acid gives DOCA.



The Cardiac Glycosides

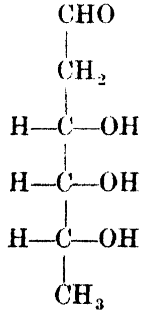
For many years the active principles of the digitalis group were classed with the alkaloids, mainly on account of their profound physiological action which, in many ways, resembles that of the alkaloids. When, however, a pure nitrogen-free crystalline principle was obtained from digitalis, it became necessary to segregate these substances from the alkaloid group, and the fact that they are capable of hydrolysis to sugar molecules and an active principle, the ' aglycone ', places them naturally among the glycosides ; since their main physiological action is on the heart they have been termed ' cardiac glycosides '.

There are three main groups—from digitalis, from squill and from strophanthus ; it is proposed to deal with each in turn.

Digitalis Glycosides

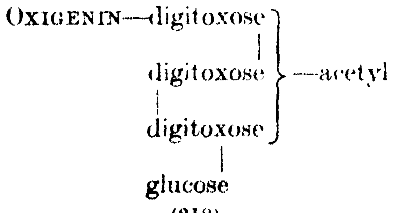
Experimental work on this group has been complicated by three factors—the large number of similar substances found together in the plant ; their lability, and the tendency which they have to form mixed crystals of definite composition amongst themselves. Thus, in the extraction of the leaves of *Digitalis lanata*, an active material (digilanid) was obtained which, on repeated crystallisation from aqueous methanol, showed no change in chemical and physical properties, but which proved nevertheless to be a mixture of three substances, separable by virtue of their differing distribution coefficients between aqueous methanol and chloroform.

The three closely related digilanids (A, B, and C) may be hydrolysed by a variety of methods, giving parallel results in each case ; thus, in faintly alkaline solution, acetic acid and a deacetyldigilanid is obtained ; enzyme action, however, splits off one molecule of glucose. The action of these two reagents is independent since, by submitting the product of either process to the other process the same product, an " oxin ", is obtained. Each " oxin " will, on acid hydrolysis, yield three molecules of digitoxose, a simple sugar having the structure (217)—



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{CH_3} \end{array}$$

(217)



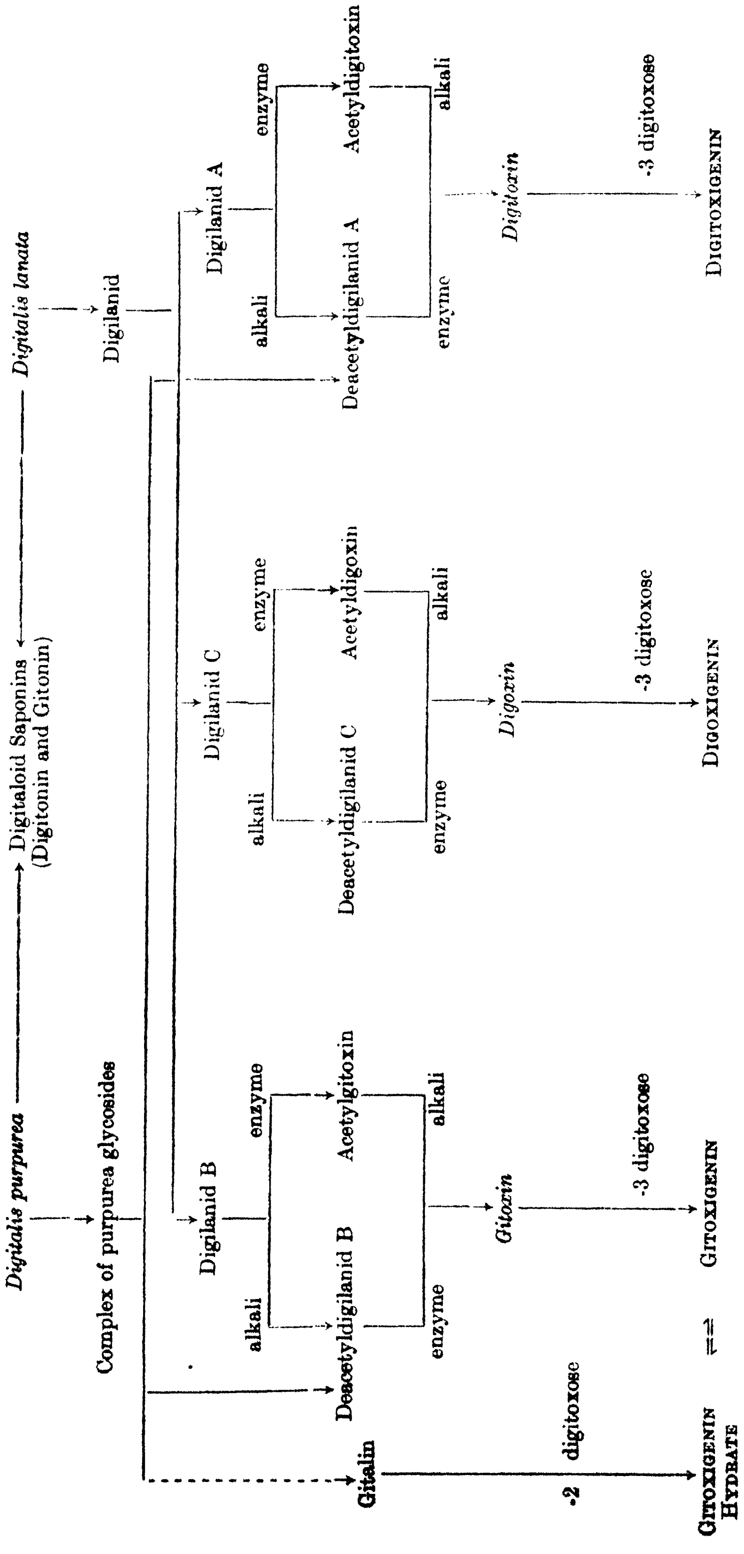
$$\begin{array}{l} \text{OXIGENIN—digitoxose} \\ \qquad\qquad\quad | \\ \qquad\qquad \text{digitoxose} \\ \qquad\qquad\quad | \\ \qquad\qquad \text{digitoxose} \\ \qquad\qquad\quad | \\ \qquad\qquad \text{glucose} \end{array} \left.\begin{array}{l} \\ \\ \\ \\ \\ \end{array}\right\}\text{—acetyl}$$

(218)

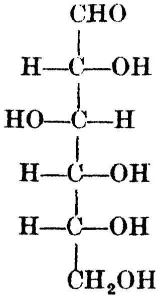
and an " oxigenin ". This degradation is shown in Table IX, together with the similar compounds from the more common *Digitalis purpurea*. Since any degree of deacetylation and/or removal of sugar may obtain in the products extracted from the leaves industrially, the variations of the natural product extend over a wide range. The general structure of a digilanid is represented by (218), the physiological properties being mainly associated with the oxigenin group.

In a similar way, squill has been made to yield a product which could be separated into a crystalline and highly physiologically active scillaren A and an, as yet, amorphous scillaren B which surpasses scillaren A in physiological

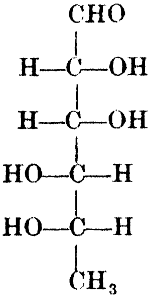
TABLE IX


Digitalis purpurea
Digitaloid Saponins
(Digitonin and Gitonin)
Digitalis lanata
Complex of purpurea glycosides
Digilanid
Digilanid B
Digilanid C
Digilanid A
alkali
enzyme
Deacetyldigilanid B
Acetylgitoxin
Deacetyldigilanid C
Acetyldigoxin
Deacetyldigilanid A
Acetyldigitoxin
Gitalin
Gitoxin
Digoxin
Digitoxin
-2 digitoxose
-3 digitoxose
Gitoxigenin Hydrate
Gitoxigenin
Digoxigenin
Digitoxigenin

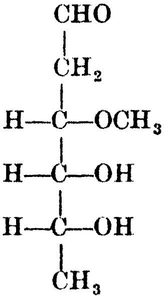
activity. The hydrolysis of scillaren A (see Table X), yields glucose, rhamnose and an aglycone scillaridin A, which has an empirical formula $C_{24}H_{30}O_3$. Further, the strophanthus series of compounds yields a series of glycosides of which cymarin is the type, which yield the sugars glucose, cymarose and/or rhamnose, and an aglycone on hydrolysis.



Glucose

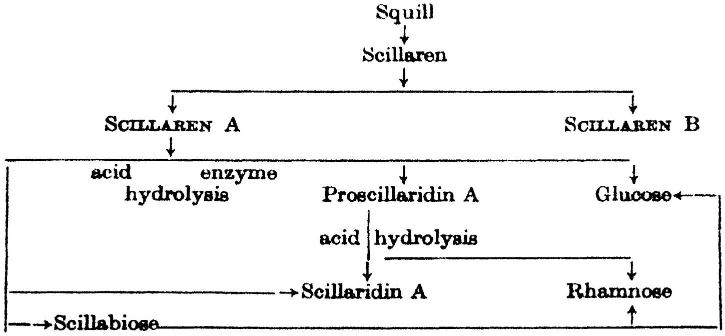


Rhamnose



Cymarose

TABLE X



The main aglycones are shown in Table XI below :—

TABLE XI

Glycoside	Aglycone			Formula of aglycone
		M.P.	$[\alpha]_D$	
			(Ethanol)	
Digilanid A Digitoxin	Digitoxigenin	253°	+ 19·1°	$C_{23}H_{34}O_4$
Digilanid B Gitoxin	Gitoxigenin	136°	+ 38·5°	$C_{23}H_{34}O_5$
Digilanid C Digoxin	Digoxigenin	222°	+ 25·8°	$C_{23}H_{34}O_5$
Scillaren A	Scillaridin A	212°	—	$C_{24}H_{30}O_3$
Cymarin *k*-Strophanthin B	Strophanthidin	1,1–175°	+ 44° (Methanol)	$C_{23}H_{32}O_6$
Ouabain	Ouabagenin			$C_{23}H_{34}O_8$
Periplocymarin	Periplogenin	?	+ 31·5	$C_{23}H_{34}O_5$
Sarmentocymarin	Sarmentogenin	265°	+ 21·5°	$C_{23}H_{34}O_5$
Uzarin	Uzarigenin			$C_{23}H_{34}O_4$
Theretin	Theretigenin			$C_{23}H_{34}O_4$

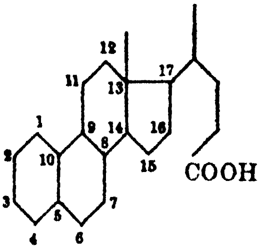
The parallel physiological activities of these substances and the palpably similar empirical formula of their aglycones led to the supposition that they were derived from a common structure. The nature of this common structure was elucidated by converting scillaridin-A by the following series of changes to *allo*-cholanic acid—

1. Scillaridin-A ($C_{24}H_{30}O_3$) was dehydrated in vacuum to
2. Anhydroscillaridin-A ($C_{24}H_{28}O_2$) which, on exhaustive hydrogenation, yielded the saturated carboxylic acid $C_{24}H_{40}O_2$, from which *allo*-cholanic acid (219) was separated by purification.

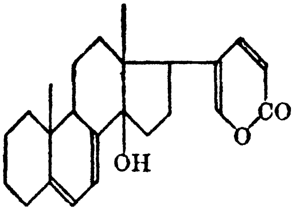
Since these reactions proceed without loss of carbon, and since there is no reason to suppose that any alteration in basic ring structure has taken place, it follows that scillaridin-A and *allo*-cholanic acid differ only in the following points :—

(*a*) the presence of unsaturation in scillaridin-A,
(*b*) the nature of the side-chain in scillaridin-A,
(*c*) the position and function of the third oxygen atom of scillaridin-A.

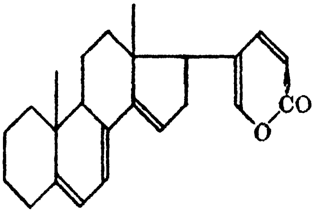
General examination shows scillaridin-A to be a lactone, and points to the existence of a free hydroxyl group in position ‘ 14 ’. The probable formulæ for scillaridin-A and its anhydro derivative are (220) and (221)—



(219)

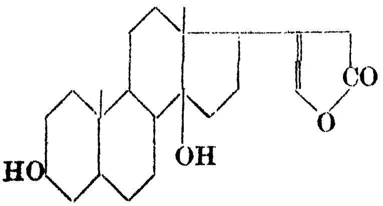


(220)

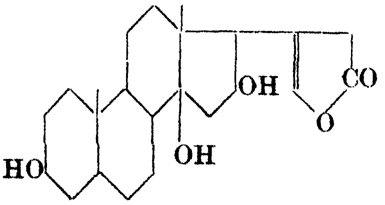


(221)

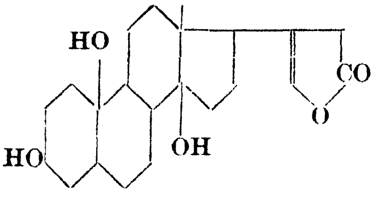
Further, Jacobs and Tschesche by dehydrogenation of strophanthidin with selenium, obtained methylcyclopentenophenanthrene, and Jacobs converted digitoxigenin to ætiocholanic acid. This, and other evidence, has led to the structures below and at top of next page for the principal cardiac aglycones :—



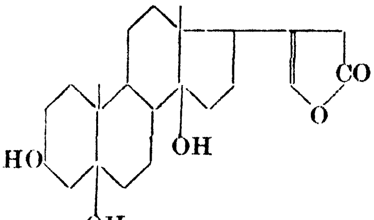
Digitoxigenin



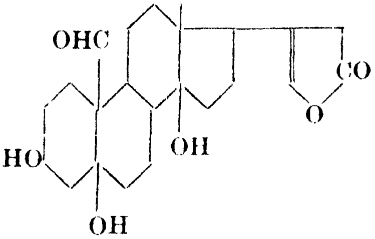
Gitoxigenin



Digoxigenin



Periplogenin



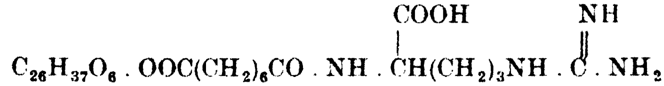
Strophanthidin

The mechanism of the attachment of the carbohydrate fractions of the original glycosides is not clear.

TOAD POISONS

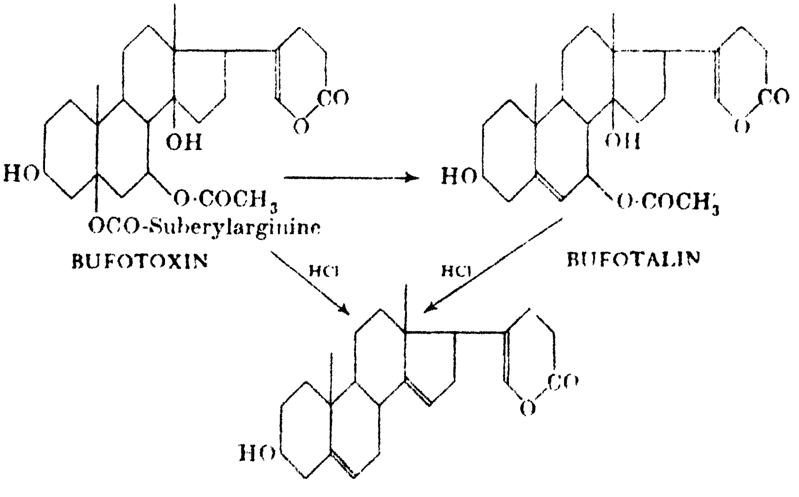
The toad has several physiologically active products in the secretion of its skin glands, including adrenalin and a cardiotonic poison which resembles digitalis in its action. This substance has been made use of in medicine from the earliest times, and is still used in China (ch'an su); in Western medicine, it has been supplanted by digitalis and squill preparations.

Bufotoxin, $C_{40}H_{62}O_{11}N_4$, from the common toad readily decomposes into bufotalin and suberylarginine, and has the formula :—[1]



$$C_{26}H_{37}O_6 \,.\, OOC(CH_2)_6CO \,.\, NH \,.\, \overset{\overset{COOH}{|}}{C}H(CH_2)_3NH \,.\, \overset{\overset{NH}{\|}}{C} \,.\, NH_2$$

The deposition is not, however, a simple hydrolysis, but involves more deep-seated changes, which may possibly be represented thus :—



BUFOTALIEN

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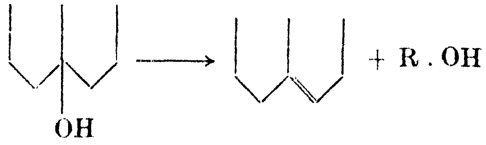
[1] Wieland, Hesse and Hüttel, *Ann.*, 1936, **524**, 203. Tschesche and Offe, *Ber.*, 1936, **69**, 2367.

It will be noted that the three stages in the degradation of bufotoxin to bufotalien involve the removal of a compound of the type R . OH from three groups comprising a tertiary carbon atom which arises by the fusion of two rings—



It is commonly found that such tertiary carbon atoms are associated with very labile groups.[1] The principal point of doubt is the position of attachment of the —O . COCH$_3$ group.

THE SAPONINS

The vegetable kingdom abounds with plants which contain complex glycosides capable of giving solutions which foam on shaking. These foam-producing substances, the saponins, are exceedingly difficult subjects for investigation on account of the obvious physical difficulties of handling their solutions, and also on account of the absence of sharp criteria of purity, and of the ease of their decomposition.

The saponins are of two main classes; those with steroid sapogenins and those with triterpenoid sapogenins. Examples of the former are digitonin, gitonin and tigonin, which accompany the cardiac glycosides of the digitalis group. When digitonin is subjected to hydrolysis, it yields four molecules of galactose, one of xylose, and a steroid sapogenin termed "digitogenin" ($C_{27}H_{44}O_5$) ; gitonin and tigonin behave similarly, and steroids are also obtained from sarsasaponin (from sarsaparilla or smilax) and other members of the series. Table XII indicates the component factors of some of the more important steroid saponins :—

TABLE XII

Saponin	Formula	Source	Genin	Formula	Carbohydrate components
Digitonin	$C_{56}H_{92}O_{29}$	Digitalis purpura	Digitogenin m. 283°	$C_{27}H_{44}O_5$	4 Galactose Xylose
Gitonin	$C_{51}H_{82}O_{23}$	Digitalis purpura	Gitogenin m. 272°	$C_{27}H_{44}O_4$	3 Galactose Pentose
Tigonin	$C_{56}H_{92}O_{27}$	Digitalis purpura Digitalis lanata	Tigogenin m. 204°	$C_{27}H_{44}O_3$	2 Glucose 2 Galactose 1 Rhamnose
Sarsasaponin	$C_{44}H_{14}O_{17}$	Sarsaparilla root	Sarsasapogenin m. 199°	$C_{27}H_{44}O_3$	2 Glucose 1 Rhamnose

All the compounds appear to be C_{27}-substances and, like cholesterol, yield a methylheptanone on oxidation ; further, Jacobs and Simpson [2] showed that dehydrogenation of a gitogenin and sarsasapogenin yields the Diels hydrocarbon.

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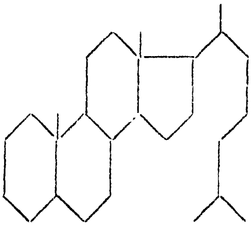
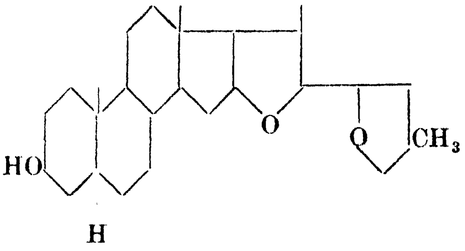
[1] See also Wieland, *Ann.*, 1936, **524**, 203 for alternative suggestions.
[2] Jacobs and Simpson, *J.A.C.S.*, 1934, **56**. 1424.

This evidence, in spite of the possibility that the methylheptanone is not identical with that from cholesterol (p. 903), led to the view that the fundamental carbon structure of the steroid sapogenins is probably (222).



(222)



(223)

The position of the oxygen atoms is in doubt, although there is much evidence leading up to the formula (223) of Tscheschc,[1] as modified by Askew, Farmer and Kon,[2] for sarsasapogenin.[3]

TRITERPENOID SAPOGENINS

The following list of triterpenoid saponins indicates the wide botanical field over which they are distributed and, even so, contains only a few typical examples—

TABLE XIII

Saponin	Sapogenin	Source
Hederin	Hederagenin (C_{30}) (+ rhamnose and arabinose)	Ivy, soap-nuts
Aescin	Aescigenin (C_{35}) (+ glucose and glucuronic acid) Tiglic acid + Aescigen (C_{30})	Horse chestnut
Oleanolin	Oleanolic acid (C_{30}) (and glucuronic acid)	Mistletoe, sugar-beet, marigold
	Oleanolic acid (C_{30})	Found free in clove and olive
Quillaia	Quillaia sapogenin	Quillaia bark (used for putting the "head" on beer and ginger-beer)

The sapogenins have a C_{30} structure and certain fundamental chemical properties in common. The first of these, observed by Ruzicka,[4] is the formation of 1, 2, 7-trimethylnaphthalene (sapotalene) on selenium dehydrogenation.

---

[1] Tschesche and Hagedorn, *Ber.*, 1935, **68**, 1412, 2127 ; 1936, **69**, 797.

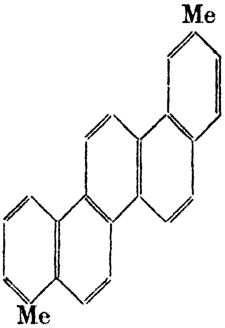
[2] Farmer and Kon, *J.C.S.*, 1937, 414 ; Askew, Farmer and Kon, *ibid.*, 1936, 1399.

[3] See also Marker *et al.*, *J.A.C.S.*, 1940, **62**, 900 for alternative structures.

[4] Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 431, 1496 ; 1934, **17**, 442 ; a bibliography will be found in Ruzicka *et al.*, Ref. No. 1 above.

In addition, the following compounds have been isolated :—

1, 2, 3, 4-Tetramethylbenzene
2, 7-Dimethylnaphthalene
1, 2, 5, 6-Tetramethylnaphthalene
1, 8-Dimethylpicene (224)



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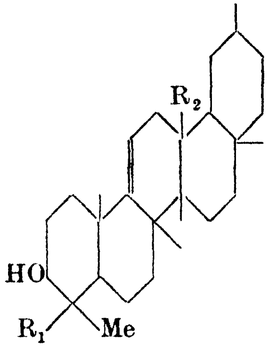


(225)

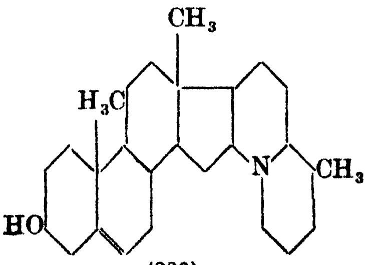
The bulk of the evidence leads to a general formula of the type (225) for the sapogenins, and the interpretation of R_1 and R_2 or various sapogenins is given in Table XIV below.

TABLE XIV

	R_1	R_2
Hederagenin	$—CH_2OH$	$—COOH$
Oleanolic acid	$—CH_3$	$—COOH$
Gypsogenin	$—CHO$	$—COOH$
Erythrodiol	$—CH_3$	$—CH_2OH$
Amyrin	$—CH_3$	$—CH_3$

The formulæ given are only provisional conjectures, but the general contour of the triterpenoid sapogenins emphasises the genetic relations between the polyterpenoids and the steroids.

It is worthy of mention that solanine, the glycoside from potato sprouts (solanine-*t*), appears to be a nitrogen containing members of the sterol group combined with one molecule each of rhamnose, glucose and galactose. The provisional formula accorded to solanidine is (226).



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APPENDIX I

LITERATURE REFERENCES

General Note

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INDEX

This index is arranged so that the prefixes (*n*-, *o*-, *p*-, *s*-, *neo*-, *iso*-, *ter*-, *sec*-, *tere*-, *ar*-, *ac*-, *cyclo*-) are ignored in forming the alphabetical arrangement. Thus, '*cyclo*Hexane' will be found under 'H' and '*iso*Valeric acid' under 'V'. The only exceptions are those cases (e.g. 'Paraconic acid' or 'Terebic acid') where the 'para' or 'tere' does not function as a prefix but forms an integral part of the name.

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